age that he regarded as prudent and wise (and there is nothing in the record to indicate that his belief in the desirability of extensive coverage was unreasonable, under the circumstances). His credit was good with banks in Oklahoma City, and he could have borrowed from banks the amounts of money needed to pay the annual premiums on his Western policies (including the six Terry Lou Lee policies) as the premiums became due in 1966 and 1967. Interest payments on such loans from banks would, of course, have been deductible for income tax purposes under 26 U.S.C. § 163(a). However, R. E. Lee would have been required to pay much higher interest rates on loans from banks than the interest rate payable on loans that were readily available to R. E. Lee, in accordance with Oklahoma law, under the terms of the Western life insurance policies. Consequently, R. E. Lee borrowed from Western, rather than from banks, the money that he needed in order to pay the insurance premiums on the Western policies, including the six Terry Lou Lee policies, as the premiums became due in 1966 and 1967. Certainly, the mere source of a loan—whether from a bank or an insurance company—should not affect the deductibility for income tax purposes of interest paid on the loan.

It is my opinion, therefore, that the portion of the $4,337.52 interest payment in 1967 that covered the interest due on the 1966 and 1967 loans from Western under the Terry Lou Lee policies was deductible in accordance with 26 U.S.C. § 163(a).

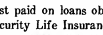
What has been said with respect to R. E. Lee's interest payment of $4,337.52 in 1967 is also applicable to the other interest payments by the plaintiffs in 1966, 1967, 1968, and 1969 that are involved in the present litigation.

To summarize: the plaintiffs are entitled to recover with respect to interest payments made during 1966–69 on loans obtained from Western during the 1966–69 period, and are not entitled to recover insofar as interest payments on loans obtained during the 1962–65 period are concerned.

CONCLUSION OF LAW

Upon the trial judge's foregoing opinion and the findings of fact, which are adopted by the court, the court concludes as a matter of law that the plaintiffs are entitled to recover (together with interest as prescribed by statute) insofar as their claims are based upon interest that was paid on loans obtained from Western Security Life Insurance Company during the years 1966, 1967, 1968, and 1969, and judgment is entered to that effect. The amount of the plaintiffs' recovery in each case will be determined in subsequent proceedings under Rule 131(c).

The court further concludes as a matter of law that the plaintiffs are not entitled to recover insofar as their claims are based upon interest paid on loans obtained from Western Security Life Insurance Company during the years 1962, 1963, 1964, and 1965, and the respective petitions are dismissed as to such claims.



Application of Stanley A. GREENFIELD and John A. DuPont.

Appeal No. 77-632.

United States Court of Customs and Patent Appeals.

March 16, 1978.

The Patent and Trademark Office Board of Appeals, serial No. 389,745, sustained examiner's rejection of certain claims of patent application for formaldehyde stabilized coating compositions, and applicants appealed. The Court of Customs and Patent Appeals, Miller, J., held that applicants' evidence was insufficient to negate prima facie obviousness of applicants' claims.

Affirmed.

1. Patents ⇐36(1)

Patent applicants failed to rebut prima facie obviousness of combining formaldehyde with certain mildewcide to prevent chemical degradation of mildewcide, in view of applicants' failure to show that mildewcide normally decomposed under claimed conditions. 35 U.S.C.A. § 103.

2. Patents ⇐112.1

Mere conclusory statements in specification, unsupported by objective evidence, are entitled to little weight when Patent and Trademark Office questions efficacy of those statements.

3. Patents ⇐32

Where Patent and Trademark Office Board of Appeals did not challenge adequacy of applicants' disclosure but only challenged adequacy of proof submitted to rebut prima facie case of obviousness, burden of proof remained on applicants and did not shift back to Patent and Trademark Office Board of Appeals. 35 U.S.C.A. § 103.

4. Patents ⇐18

Objective evidence of nonobviousness must be commensurate in scope with claims which evidence is offered to support. 35 U.S.C.A. § 103.

5. Patents ⇐113(6)

Arguments of counsel cannot take place of evidence in patent application proceedings.

Franklin D. Wolffe, Fidelman, Wolffe & Waldron, Washington, D. C., attorneys of record, for appellants.

Joseph F. Nakamura, Washington, D. C., for the Commissioner of Patents; Henry W. Tarring, II, Washington, D. C., of counsel.

Before MARKEY, Chief Judge, and RICH, BALDWIN, LANE and MILLER, Judges.

MILLER, Judge.

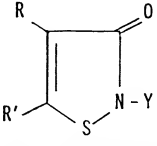
This is an appeal from the decision of the Patent and Trademark Office ("PTO") Board of Appeals ("board") sustaining the examiner's rejection of claims 6, 7, and 9 of application serial No. 389,745, filed August 20, 1973, for "Formaldehyde Stabilized Coating Compositions." We affirm.

BACKGROUND

The Invention

The claimed subject matter is directed to a paint composition comprising an acrylic polymer in a water carrier containing a 3-isothiazolone as a mildewcide and *formaldehyde as a stabilizer for the 3-isothiazolone*, which composition has been neutralized to a pH of 6.0 to 9.2 with ammonia or an amine. The 3-isothiazolone prevents mildew growth in the dry paint film on the organic binder material of the coating; the formaldehyde stabilizes the 3-isothiazolone against degradation, which occurs under alkaline conditions in the latex form (in the paint can). The claims on appeal are:

6.[1] In a coating composition which comprises a film-forming acrylic emulsion polymer, a water carrier and a 3-isothiazolone having the formula:



wherein Y is a hydrogen atom, a (C_1–C_{18}) alkyl group, a (C_6–C_{10}) aryl group, or a (C_7–C_{10}) aralkyl group;

R is a hydrogen atom, a halogen atom, or a (C_1–C_4) alkyl group, and

R' is a hydrogen atom, a halogen atom, or a (C_1–C_4) alkyl group, and

1. For the sake of a clarity, claim 6, which is dependent from a number of nonappealed claims, has been rewritten in complete form.

wherein the composition is neutralized to a pH of about 6.0 to about 9.2 with ammonia or an organic amine;
wherein the composition further comprises a stabilizing amount of formaldehyde present in an amount equivalent to about 0.5 to about 20 pounds of 37% aqueous formaldehyde per 100 gallons of the composition;
the ammonia or amine is present in an amount of about 0.25 to about 10 pounds per 100 gallons of the composition, and the isothiazolone is present in an amount of about 0.1 to about 20 pounds per 100 gallons of the composition.

7. The composition of claim 6 wherein Y is a hydrogen atom or an unsubstituted (C_1–C_{18}) alkyl group, R is a hydrogen atom, and R' is a hydrogen atom.

9. The composition of claim 6 wherein Y is a hydrogen atom or a (C_1–C_{18}) alkyl group, R is a hydrogen atom, and R' is a halogen atom.

Proceedings Below

The claims[2] were rejected under 35 U.S.C. § 103 over either of two Lewis et al. patents, '121[3] or '488,[4] in combination with Walker.[5] The Lewis patents disclose several 3-isothiazolones, including those of the appealed claims. Lewis '131 discloses the use of 3-isothiazolones in conjunction with other biocides; Lewis '488 discloses their use as mildewcides in acrylic, water-based paints. Walker discloses the use of formaldehyde as a biocide, particularly as a disinfectant which does not harm paint.

The board found that the Lewis patents and Walker show that both 3-isothiazolones and formaldehyde are known to be useful as biocides in coating compositions. It concluded that since the Lewis patents disclose that 3-isothiazolones "may be utilized as the sole biocidal agents or may be used in conjunction with other fungicides, insecticides, miticides and comparable pesticides," it would have been *prima facie* obvious to combine the 3-isothiazolones of the Lewis patents with formaldehyde. Furthermore, according to the board, the mere fact that appellants "observed" that formaldehyde stabilizes the 3-isothiazolones is not sufficient to negate the *prima facie* obviousness of combining two known biocides, since appellants have not established that chemical degradation was even a problem with respect to all 3-isothiazolones under the claimed conditions.

Upon reconsideration, the board reversed the rejection of claim 8, because there was ample evidence that the claimed 3-isothiazolone species (2-*n*-octyl-3-isothiazolone) has a degradation problem, but it adhered to its decision that the *prima facie* case had not been rebutted with respect to the other claims.

OPINION

In this appeal, appellants have acknowledged that the appealed claims would have been *prima facie* obvious over the Lewis patents and Walker. Therefore, the sole issue for resolution is whether appellants have rebutted this *prima facie* case. See *In re Rinehart*, 531 F.2d 1048, 1052, 189 USPQ 143, 147 (Cust. & Pat.App.1976).

Appellants argue that the *prima facie* case is rebutted by a showing that, under the claimed pH conditions, 3-isothiazolones normally decompose, but that they do not do so when formaldehyde is added to the composition; that is, the presence of the formaldehyde in the paint compositions has the unexpected property of stabilizing the 3-isothiazolones. However, the validity of the argument depends on whether it has been demonstrated that the claimed 3-

2. Although the board affirmed the rejection of claims 1–7 and 9–19, an appeal has been taken only with respect to claims 6, 7, and 9. The board reversed the rejection of claim 8.

3. Patent No. 3,523,121, issued August 4, 1970, for "Certain 2-Carbamoyl-3-isothiazolenes."

4. Patent No. 3,761,488, issued September 25, 1973, for "3-Isothiazolones."

5. Walker, "Formaldehyde," *American Chemical Society Monograph Series No. 159* at 569–74 (3d ed. 1964).

isothiazolones normally decompose under the claimed conditions.[6]

[1, 2] Appellants have submitted no objective evidence to demonstrate the existence of a degradation problem of 3-isothiazolones and rely solely on their specification. Six of the seven examples recite the stabilizing effects on 2-*n*-octyl-3-isothiazolone (the compound of allowed claim 8) of formaldehyde in various paint compositions;[7] specific test results demonstrate the stabilizing effects.[8] The only mention in the entire specification of any other 3-isothiazolone is in Example 6, which states that "[f]ormulations are prepared in which the isothiazolone of Formulation I is replaced by:" followed by a recitation of nine 3-isothiazolones. The example continues:

> In the above formulations, when formaldehyde or a compound which releases formaldehyde under basic conditions is present in the formulation, the formulation is stabilized against decomposition of the isothiazolone. However, when formaldehyde or formaldehyde-releasing agent is absent, decomposition of the isothiazolone occurs on storage.

As is evident, there is no recitation of the conditions[9] under which these "formulations" were tested,[10] and there is no factual support for the general allegation that unexpected results were obtained. No specific test results regarding these "formulations" are disclosed. Accordingly, appellants have not rebutted the PTO's *prima facie* case. *In re Hyson*, 453 F.2d 764, 59 CCPA 782, 172 USPQ 399 (1972). Mere conclusory statements in the specification, unsupported by objective evidence, are entitled to little weight when the PTO questions the efficacy of those statements. *In re Lindner*, 457 F.2d 506, 59 CCPA 920, 173 USPQ 356 (1972),[11] and cases cited therein.

[3] Appellants argue that the burden is upon the PTO to present evidence that the claimed 3-isothiazolones do not decompose, analogizing the rejection to a finding of insufficient disclosure under section 112. If appellants had established that several of the species within claims 7 and 9 were subject to decomposition or if they had provided, *with supporting evidence*, some scientific basis to explain why all 3-isothiazolones would decompose under the claimed conditions, they would have a basis for arguing that the burden has been shifted back to the PTO. But in this section 103 rejection, the board has not challenged the

6. We are inclined to agree with appellants that, if the record establishes that formaldehyde stabilizes the claimed 3-isothiazolones under the claimed conditions, the *prima facie* case would be rebutted. *In re Nolan*, 553 F.2d 1261, 193 USPQ 641 (Cust. & Pat.App.1977); *In re Albrecht*, 514 F.2d 1385, 185 USPQ 585 (Cust. & Pat.App.1975); *In re Murch*, 464 F.2d 1051, 59 CCPA 1277, 175 USPQ 89 (1972). The board indicated that this stabilizing property would be sufficient to rebut the *prima facie* case in its reversal of the rejection of claim 8, for which it found sufficient evidence that the claimed 3-isothiazolone normally decomposes under the claimed conditions in the absence of formaldehyde.

7. A footnote to Example 1 suggests that 5-chloro-2-*n*-octyl-3-isothiazolone was also tested; however, no specific test results are disclosed.

8. Sample No. 1 (a relatively impure sample of the 3-isothiazolone) discloses that there was 41% degradation after 90 days, when no formaldehyde was added, but when the formaldehyde level was 20, there was only 12% degradation.

9. Although the disclosure does recite "basic" conditions, this generalized disclosure is insufficient, particularly in light of the specification's statement that degradation occurs under "*highly basic* conditions."

10. Appellants argue that the "normal reading of this Example is that the conditions of Example 1 are repeated, save for the substitution of the specific isothiazolone"; hence, the conditions of Example 1 are incorporated into Example 6. Although the example could have been so worded, it was not. This example refers only to "Formulation 1" which was *used* in Example 1, but there is no implication that the conditions of Example 1 are the same in all examples using Formulation 1. We note that Example 2 uses Formulation 1, but separate testing conditions are recited.

11. This case is strongly reminiscent of *Lindner*, where only one mixture of the ingredients was tested; yet the specification contained broad conclusory statements regarding other mixtures which were also within the scope of the claims.

adequacy of appellants' disclosure—only the adequacy of the proof submitted to rebut the PTO's *prima facie* case.

[4] In summary, the specification discloses test results of the stabilizing effects of only one 3–isothiazolone (and generalized conclusions regarding a few other species) [12] of a claimed subgenus which consists of several hundred compounds.[13] Establishing that one (or a *small* number of) species gives unexpected results is inadequate proof, for "it is the view of this court that objective evidence of non-obviousness must be commensurate in scope with the claims which the evidence is offered to support." *In re Tiffin*, 448 F.2d 791, 792, 58 CCPA 1420, 1421, 171 USPQ 294 (1971); [14] *In re Lindner, supra.* This court's conclusion in *Lindner, supra*, 457 F.2d at 508, 59 CCPA at 923, 173 USPQ at 358, is equally pertinent here:

> Here only one mixture of ingredients was tested . . . . This particular mixture was found to produce a good dispersion with refractory 7–21–7 fertilizer solutions. As the board noted, the specification also indicates that the same mixture was successfully used with 7–21–7 fertilizer solutions. The claims, however, are much broader in scope, covering mixtures of numerous compounds, and we have to agree with the Patent Office that *there is no "adequate basis for reasonably concluding that the great number and variety of compositions included by the claims would behave in the same manner as the [single] test composition."* [Citation omitted; emphasis added.]

[5] Regarding appellants' argument that it is "believed obvious" that the substituents linked to the heterocyclic ring would not be *expected* to affect decomposition, but rather the more reactive members of the ring (S, N, and O atoms) would be the location of the decomposition, there simply is no supporting evidence.[15] And arguments of counsel cannot take the place of evidence.[16] *In re Pearson*, 494 F.2d 1399, 181 USPQ 641 (Cust. & Pat.App.1974).

In view of the foregoing, the decision of the board is *affirmed.*

AFFIRMED.

12. The specification recites a total of five species which are encompassed within claim 7. Only two of the species of claim 9 are recited. All nine of the species of Example 6 are within the scope of claim 6; however, the breadth of claim 6 is such that it encompasses literally thousands of compounds.

13. Contrary to appellants' suggestion, each of the claimed subgenuses encompasses hundreds of compounds, since the (C1–C18) alkyl chains may be branched.

14. In *Tiffin*, the *prima facie* case was rebutted by a showing of commercial success in regard to those claims limited to "cups." But where the claims were broader (to "containers"), the court held that the proof was insufficient to rebut the *prima facie* case.

15. A further argument of appellants is that any compound which stabilizes the species of claim 8 would also stabilize the other claimed 3–isothiazolones. However, their burden of showing *unexpected* results cannot be satisfied by establishing that one species decomposes under the claimed conditions, coupled with a mere *expectation* that all related compounds will also decompose under similar conditions.

16. Nor is this the type of matter which is the proper subject of judicial notice. *In re Barr*, 444 F.2d 588, 591 n. 5, 58 CCPA 1388, 1395 n. 5, 170 USPQ 330, 334 n. 5 (1971).

LEXSEE 127 S.CT. 1727

KSR INTERNATIONAL CO., Petitioner v. TELEFLEX INC. et al.

No. 04-1350

SUPREME COURT OF THE UNITED STATES

550 U.S. 398; 127 S. Ct. 1727; 167 L. Ed. 2d 705; 2007 U.S. LEXIS 4745; 75 U.S.L.W. 4289; 82 U.S.P.Q.2D (BNA) 1385; 20 Fla. L. Weekly Fed. S 248

November 28, 2006, Argued
April 30, 2007, Decided

SUBSEQUENT HISTORY:
On remand at *Teleflex, Inc. v. KSR Int'l Co., 228 Fed. Appx. 988, 2007 U.S. App. LEXIS 16051 (Fed. Cir., June 20, 2007)*

PRIOR HISTORY: ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT.
Teleflex, Inc. v. KSR Int'l Co., 119 Fed. Appx. 282, 2005 U.S. App. LEXIS 176 (Fed. Cir., 2005)

DISPOSITION: Reversed and remanded.

CASE SUMMARY:

PROCEDURAL POSTURE: Respondent, licensees of a patent, alleged that petitioner, a competitor, infringed the licensees' patent for an accelerator pedal assembly for vehicles, but the competitor asserted that the patent claim in dispute was invalid as obvious under *35 U.S.C.S. § 103*. Upon the grant of a writ of certiorari, the competitor appealed the judgment of the U.S. Court of Appeals for the Federal Circuit which reversed a summary judgment of patent invalidity.

OVERVIEW: To satisfy customer needs, the competitor modified its design for an adjustable pedal system for vehicles with cable-actuated throttles by adding a modular sensor to make the system compatible with vehicles using computer-controlled throttles. The licensees contended that the competitor infringed the patent claim of a position-adjustable pedal assembly with an electronic pedal position sensor attached a fixed pivot point. The U.S. Supreme Court unanimously held that the patent claim was invalid as obvious since mounting an available sensor on a fixed pivot point of the competitor's pedal was a design step well within the grasp of a person of ordinary skill in the relevant art, and the benefit of doing so was obvious. The marketplace created a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for doing so. Further, the problem to be solved by the patent claim did not limit its application as prior art, the competitor's showing that it was obvious to try a combination of elements sufficiently supported the finding of obviousness, and the claim was the result of ordinary skill and common sense rather than innovation.

OUTCOME: The judgment reversing the summary judgment of invalidity was reversed, and the case was remanded for further proceedings.

LexisNexis(R) Headnotes

Patent Law > Nonobviousness > General Overview

[HN1] *35 U.S.C.S. § 103* forbids issuance of a patent when the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

Patent Law > Nonobviousness > Elements & Tests > Prior Art

Patent Law > Nonobviousness > Elements & Tests > Secondary Considerations

[HN2] Under *35 U.S.C.S. § 103*, the scope and content of prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. While the sequence of these questions might be reordered in any particular case, the factors continue to define the inquiry that controls. If a court, or patent examiner, conducts this analysis and concludes the claimed subject matter was obvious, the claim is invalid under *§ 103*.

Patent Law > Infringement Actions > Defenses > Patent Invalidity > Validity Presumption

[HN3] By direction of *35 U.S.C.S. § 282*, an issued patent is presumed valid.

Patent Law > Nonobviousness > Elements & Tests > Predictability

[HN4] A patent for a combination which only unites old elements with no change in their respective functions obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men. This is a principal reason for declining to allow patents for what is obvious. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.

Patent Law > Nonobviousness > Elements & Tests > Predictability

[HN5] When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, *35 U.S.C.S. § 103* likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. A court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

Patent Law > Nonobviousness > Elements & Tests > General Overview

[HN6] Rejection of a patent on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness. However, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

Patent Law > Nonobviousness > Elements & Tests > Prior Art

[HN7] A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

Patent Law > Nonobviousness > Elements & Tests > Secondary Considerations

[HN8] The obviousness analysis in the patent context

cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility.

Patent Law > Nonobviousness > Elements & Tests > Manner of Conception
Patent Law > Nonobviousness > Elements & Tests > Predictability

[HN9] In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under *35 U.S.C.S. § 103*. One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard

[HN10] A problem motivating a patentee may be only one of many addressed by the patent's subject matter. The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art.

Patent Law > Nonobviousness > Elements & Tests > Ordinary Skill Standard

[HN11] When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under *35 U.S.C.S. § 103*.

Patent Law > Nonobviousness > Elements & Tests > Hindsight

[HN12] In a patent obviousness case, a factfinder must be aware of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning. Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under U.S. Supreme Court case law nor consistent with it.

Patent Law > Infringement Actions > Summary Judgment > General Overview
Patent Law > Nonobviousness > Elements & Tests > General Overview
Patent Law > Nonobviousness > Evidence & Procedure > Fact & Law Issues

[HN13] In considering summary judgment on a question of patent obviousness, a district court can and should take into account expert testimony, which may resolve or keep open certain questions of fact. That is not the end of the issue, however. The ultimate judgment of obviousness is a legal determination. Where the content of the prior art, the scope of the patent claim, and the level of ordinary skill in the art are not in material dispute, and the obviousness of the claim is apparent in light of these factors, summary judgment is appropriate.

Constitutional Law > Congressional Duties & Powers > Copyright & Patent Clause
Patent Law > Nonobviousness > Elements & Tests > General Overview

[HN14] As progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws. Were it otherwise patents might stifle, rather than promote, the progress of useful arts. *U.S. Const. art. I, § 8, cl. 8*. These premises lead to the bar on patents claiming obvious subject matter established by case law and codified in *35 U.S.C.S. § 103*. Application of the bar must not be confined within a test or formulation too constrained to serve its purpose.

DECISION:

[***705] Company that added modular sensor to its automobile-accelerator-pedal system held entitled to summary judgment in infringement action by holder of

license for patent covering assembly with electronic sensor, as pertinent claim was "obvious" within meaning of *35 U.S.C.S. § 103*.

SUMMARY:

Procedural posture: Respondent, licensees of a patent, alleged that petitioner, a competitor, infringed the licensees' patent for an accelerator pedal assembly for vehicles, but the competitor asserted that the patent claim in dispute was invalid as obvious under *35 U.S.C.S. § 103*. Upon the grant of a writ of certiorari, the competitor appealed the judgment of the U.S. Court of Appeals for the Federal Circuit which reversed a summary judgment of patent invalidity.

Overview: To satisfy customer needs, the competitor modified its design for an adjustable pedal system for vehicles with cable-actuated throttles by adding a modular sensor to make the system compatible with vehicles using computer-controlled throttles. The licensees contended that the competitor infringed the patent claim of a position-adjustable pedal assembly with an electronic pedal position sensor attached a fixed pivot point. The U.S. Supreme Court unanimously held that the patent claim was invalid as obvious since mounting an available sensor on a fixed pivot point of the competitor's pedal was a design step well within the grasp of a person of ordinary skill in the relevant art, and the benefit of doing so was obvious. The marketplace created a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for doing so. Further, the problem to be solved by the patent claim did not limit its application as prior art, the competitor's showing that it was obvious to try a combination of elements [***706] sufficiently supported the finding of obviousness, and the claim was the result of ordinary skill and common sense rather than innovation.

Outcome: The judgment reversing the summary judgment of invalidity was reversed, and the case was remanded for further proceedings.

LAWYERS' EDITION HEADNOTES:

[***LEdHN1]

PATENTS § 19.1

PATENTABILITY -- OBVIOUSNESS OF SUBJECT MATTER

Headnote:[1]

35 U.S.C.S. § 103 forbids issuance of a patent when the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.

[***LEdHN2]

PATENTS § 19 PATENTS § 19.1

PATENTABILITY -- MECHANICAL SKILL -- OBVIOUSNESS OF SUBJECT MATTER

Headnote:[2]

Under *35 U.S.C.S. § 103*, the scope and content of prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented. While the sequence of these questions might be reordered in any particular case, the factors continue to define the inquiry that controls. If a court, or patent examiner, conducts this analysis and concludes the claimed subject matter was obvious, the claim is invalid under *§ 103*.

[***LEdHN3]

EVIDENCE § 333

PATENT -- PRESUMPTION OF VALIDITY

Headnote:[3]

By direction of *35 U.S.C.S. § 282*, an issued patent is presumed valid.

[***LEdHN4]

PATENTS § 37

PATENTABILITY -- COMBINATION OF OLD ELEMENTS

Headnote:[4]

A patent for a combination which only unites old elements with no change in their respective functions obviously withdraws what is already known into the field of its monopoly and diminishes the resources available to skillful men. This is a principal reason for declining to allow patents for what is obvious. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results.

[***LEdHN5]

PATENTS § 50

PATENTABILITY -- OBVIOUSNESS OF IMPROVEMENT

Headnote:[5]

When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, *35 U.S.C.S. § 103* likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. A court must ask whether the [***707] improvement is more than the predictable use of prior art elements according to their established functions.

[***LEdHN6]

PATENTS § 19.1

PATENTABILITY -- OBVIOUSNESS OF SUBJECT MATTER

Headnote:[6]

Rejection of a patent on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support a legal conclusion of obviousness. However, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

[***LEdHN7]

PATENTS § 19.1

PATENTABILITY -- COMPOSITION OF ELEMENTS -- OBVIOUSNESS

Headnote:[7]

A patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity will be combinations of what, in some sense, is already known.

[***LEdHN8]

PATENTS § 19.1

PATENTABILITY -- OBVIOUSNESS OF TECHNIQUES OR COMBINATIONS -- SCIENTIFIC LITERATURE

Headnote:[8]

The obviousness analysis in the patent context cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility.

[***LEdHN9]

PATENTS § 19.1

PATENTABILITY -- SUBJECT MATTER -- DETERMINATION WHETHER OBVIOUS

Headnote:[9]

In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under *35 U.S.C.S. § 103*. One of the ways in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

[***LEdHN10]

PATENTS § 19.1

PATENTABILITY -- OBVIOUSNESS

Headnote:[10]

A problem motivating a patentee may be only one of many addressed by the patent's subject matter. The question is not whether the combination was obvious to the patentee [***708] but whether the combination was obvious to a person with ordinary skill in the art.

[***LEdHN11]

PATENTS § 19 PATENTS § 19.1

PATENTABILITY -- ORDINARY SKILL -- OBVIOUSNESS

Headnote:[11]

When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under *35 U.S.C.S. § 103*.

[***LEdHN12]

PATENTS § 19.1

PATENTABILITY -- OBVIOUSNESS

Headnote:[12]

In a patent obviousness case, a factfinder must be aware of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning. Rigid preventative rules that deny factfinders recourse to common sense, however, are neither necessary under U.S. Supreme Court case law nor consistent with it.

[***LEdHN13]

SUMMARY JUDGMENT AND JUDGMENT ON PLEADINGS § 5

PATENTABILITY -- OBVIOUSNESS OF CLAIM -- SUMMARY JUDGMENT

Headnote:[13]

In considering summary judgment on a question of patent obviousness, a district court can and should take into account expert testimony, which may resolve or keep open certain questions of fact. That is not the end of the issue, however. The ultimate judgment of obviousness is a legal determination. Where the content of the prior art, the scope of the patent claim, and the level of ordinary skill in the art are not in material dispute, and the obviousness of the claim is apparent in light of these factors, summary judgment is appropriate.

[***LEdHN14]

PATENTS § 17 PATENTS § 19.1

PATENTABILITY -- ORDINARY INNOVATION -- OBVIOUS SUBJECT MATTER

Headnote:[14]

As progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws. Were it otherwise patents might stifle, rather than promote, the progress of useful arts. *U.S. Const. art. I, § 8, cl. 8*. These premises lead to the bar on patents claiming obvious subject matter established by case law and codified in *35 U.S.C.S. § 103*. Application of the bar must not be confined within a

test or formulation too constrained to serve its purpose.

SYLLABUS

[***709] To control a conventional automobile's speed, the driver depresses or releases the gas pedal, which interacts with the throttle via a cable or other mechanical link. Because the pedal's position in the footwell normally cannot be adjusted, a driver wishing to be closer or farther from it must either reposition himself in the seat or move the seat, both of which can be imperfect solutions for smaller drivers in cars with deep footwells. This prompted inventors to design and patent pedals that could be adjusted to change their locations. The Asano patent reveals a support structure whereby, when the pedal location is adjusted, one of the pedal's pivot points stays fixed. Asano is also designed so that the force necessary to depress the pedal is the same regardless of location adjustments. The Redding patent reveals a different, sliding mechanism where both the pedal and the pivot point are adjusted.

In newer cars, computer-controlled throttles do not operate through force transferred from the pedal by a mechanical link, but open and close valves in response to electronic signals. For the computer to know what is happening with the pedal, an electronic sensor must translate the mechanical operation into digital data. Inventors had obtained a number of patents for such sensors. The so-called *'936 patent* taught that it was preferable to detect the pedal's position in the pedal mechanism, not in the engine, so the patent disclosed a pedal with an electronic sensor on a pivot point in the pedal assembly. The Smith patent taught that to prevent the wires connecting the sensor to the computer from chafing and wearing out, the sensor should be put on a fixed part of the pedal assembly rather than in or on the pedal's footpad. Inventors had also patented self-contained modular sensors, which can be taken off the shelf and attached to any mechanical pedal to allow it to function with a computer-controlled throttle. The *'068 patent* disclosed one such sensor. Chevrolet also manufactured trucks using modular sensors attached to the pedal support bracket, adjacent to the pedal and engaged [***710] with the pivot shaft about which the pedal rotates. Other patents disclose electronic sensors attached to adjustable pedal assemblies. For example, the Rixon patent locates the sensor in the pedal footpad, but is known for wire chafing.

After petitioner KSR developed an adjustable pedal system for cars with cable-actuated throttles and obtained its *'986 patent* for the design, General Motors Corporation (GMC) chose KSR to supply adjustable pedal systems for trucks using computer-controlled throttles. To make the *'986* pedal compatible with the trucks, KSR added a modular sensor to its design. Respondents (Teleflex) hold the exclusive license for the Engelgau patent, claim 4 of which discloses a position-adjustable pedal assembly with an electronic pedal position sensor attached to a fixed pivot point. Despite having denied a similar, broader claim, the U. S. Patent and Trademark Office (PTO) had allowed claim 4 because it included the limitation of a fixed pivot position, which distinguished the design from Redding's. Asano was neither included among the Engelgau patent's prior art references nor mentioned in the patent's prosecution, and the PTO did not have before it an adjustable pedal with a fixed pivot point. After learning of KSR's design for GMC, Teleflex sued for infringement, asserting that KSR's pedal system infringed the Engelgau patent's claim 4. KSR countered that claim 4 was invalid under *§ 103* of the Patent Act, which forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art."

Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545, set out an objective analysis for applying *§ 103*: "[T]he scope and content of the prior art are . . . determined; differences between the prior art and the claims at issue are . . . ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." While the sequence of these questions might be reordered in any particular case, the factors define the controlling inquiry. However, seeking to resolve the obviousness question with more uniformity and consistency, the Federal Circuit has employed a "teaching, suggestion, or motivation" (TSM) test, under which a patent claim is only proved obvious if the prior art, the problem's nature, or the knowledge of a person having ordinary skill in the art reveals some motivation or suggestion to combine the

prior art teachings.

The District Court granted KSR summary judgment. After reviewing pedal design history, the Engelgau patent's scope, and the relevant prior art, the court considered claim 4's validity, applying *Graham*'s framework to determine whether under summary-judgment standards KSR had demonstrated that claim 4 was obvious. The court found "little difference" between the prior art's teachings and claim 4: Asano taught everything contained in the claim except [***711] using a sensor to detect the pedal's position and transmit it to a computer controlling the throttle. That additional aspect was revealed in, *e.g.*, the *'068 patent* and Chevrolet's sensors. The court then held that KSR satisfied the TSM test, reasoning (1) the state of the industry would lead inevitably to combinations of electronic sensors and adjustable pedals, (2) Rixon provided the basis for these developments, and (3) Smith taught a solution to Rixon's chafing problems by positioning the sensor on the pedal's fixed structure, which could lead to the combination of a pedal like Asano with a pedal position sensor.

Reversing, the Federal Circuit ruled the District Court had not applied the TSM test strictly enough, having failed to make findings as to the specific understanding or principle within a skilled artisan's knowledge that would have motivated one with no knowledge of the invention to attach an electronic control to the Asano assembly's support bracket. The Court of Appeals held that the District Court's recourse to the nature of the problem to be solved was insufficient because, unless the prior art references addressed the precise problem that the patentee was trying to solve, the problem would not motivate an inventor to look at those references. The appeals court found that the Asano pedal was designed to ensure that the force required to depress the pedal is the same no matter how the pedal is adjusted, whereas Engelgau sought to provide a simpler, smaller, cheaper adjustable electronic pedal. The Rixon pedal, said the court, suffered from chafing but was not designed to solve that problem and taught nothing helpful to Engelgau's purpose. Smith, in turn, did not relate to adjustable pedals and did not necessarily go to the issue of motivation to attach the electronic control on the pedal assembly's support bracket. So interpreted, the court held, the patents would not have led a person of ordinary skill to put a sensor on an Asano-like pedal. That it might have been obvious to try that combination was likewise irrelevant. Finally, the court held that genuine issues of material fact precluded summary judgment.

Held:

The Federal Circuit addressed the obviousness question in a narrow, rigid manner that is inconsistent with *§ 103* and this Court's precedents. KSR provided convincing evidence that mounting an available sensor on a fixed pivot point of the Asano pedal was a design step well within the grasp of a person of ordinary skill in the relevant art and that the benefit of doing so would be obvious. Its arguments, and the record, demonstrate that the Engelgau patent's claim 4 is obvious. Pp. 11-24.

1. *Graham* provided an expansive and flexible approach to the obviousness question that is inconsistent with the way the Federal Circuit applied its TSM test here. Neither *§ 103*'s enactment nor *Graham*'s analysis disturbed the Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art. See *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152, 71 S. Ct. 127, 95 L. Ed. 162, 1951 Dec. Comm'r Pat. 572* Such a combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. See, *e.g., United States v. Adams, 383 U.S. 39, 50-52, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293* When a work is available in one field, design incentives and other market forces [***712] can prompt variations of it, either in the same field or in another. If a person of ordinary skill in the art can implement a predictable variation, and would see the benefit of doing so, *§ 103* likely bars its patentability. Moreover, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond that person's skill. A court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions. Following these principles may be difficult if the claimed subject matter involves more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. To determine whether there was an apparent reason to combine the known elements in the way a patent claims, it will often be necessary to look to interrelated teachings of multiple patents; to the effects of

demands known to the design community or present in the marketplace; and to the background knowledge possessed by a person having ordinary skill in the art. To facilitate review, this analysis should be made explicit. But it need not seek out precise teachings directed to the challenged claim's specific subject matter, for a court can consider the inferences and creative steps a person of ordinary skill in the art would employ. Pp. 11-14.

(b) The TSM test captures a helpful insight: A patent composed of several elements is not proved obvious merely by demonstrating that each element was, independently, known in the prior art. Although common sense directs caution as to a patent application claiming as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the art to combine the elements as the new invention does. Inventions usually rely upon building blocks long since uncovered, and claimed discoveries almost necessarily will be combinations of what, in some sense, is already known. Helpful insights, however, need not become rigid and mandatory formulas. If it is so applied, the TSM test is incompatible with this Court's precedents. The diversity of inventive pursuits and of modern technology counsels against confining the obviousness analysis by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasizing the importance of published articles and the explicit content of issued patents. In many fields there may be little discussion of obvious techniques or combinations, and market demand, rather than scientific literature, may often drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, for patents combining previously known elements, deprive prior inventions of their value or utility. Since the TSM test was devised, the Federal Circuit doubtless has applied it in accord with these principles in many cases. There is no necessary inconsistency between the test and the *Graham* analysis. But a court errs where, as here, it transforms general principle into a rigid rule limiting the obviousness inquiry. Pp. 14-15.

(c) The flaws in the Federal Circuit's analysis relate mostly to its [***713] narrow conception of the obviousness inquiry consequent in its application of the TSM test. The Circuit first erred in holding that courts and patent examiners should look only to the problem the patentee was trying to solve. Under the correct analysis, any need or problem known in the field and addressed by the patent can provide a reason for combining the elements in the manner claimed. Second, the appeals court erred in assuming that a person of ordinary skill in the art attempting to solve a problem will be led only to those prior art elements designed to solve the same problem. The court wrongly concluded that because Asano's primary purpose was solving the constant ratio problem, an inventor considering how to put a sensor on an adjustable pedal would have no reason to consider putting it on the Asano pedal. It is common sense that familiar items may have obvious uses beyond their primary purposes, and a person of ordinary skill often will be able to fit the teachings of multiple patents together like pieces of a puzzle. Regardless of Asano's primary purpose, it provided an obvious example of an adjustable pedal with a fixed pivot point, and the prior art was replete with patents indicating that such a point was an ideal mount for a sensor. Third, the court erred in concluding that a patent claim cannot be proved obvious merely by showing that the combination of elements was obvious to try. When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. Finally, the court drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias. Rigid preventative rules that deny recourse to common sense are neither necessary under, nor consistent with, this Court's case law. Pp. 15-18.

2. Application of the foregoing standards demonstrates that claim 4 is obvious. Pp. 18-23.

(a) The Court rejects Teleflex's argument that the Asano pivot mechanism's design prevents its combination with a sensor in the manner claim 4 describes. This argument was not raised before the District Court, and it is unclear whether it was raised before the Federal Circuit. Given the significance of the District Court's finding that combining Asano with a pivot-mounted pedal position sensor fell within claim 4's scope, it is apparent that Teleflex would have made clearer challenges if it intended to preserve this claim. Its failure to clearly raise the argument, and the appeals court's silence on the issue, lead this Court to accept the District

Court's conclusion. Pp. 18-20.

(b) The District Court correctly concluded that when Engelgau designed the claim 4 subject matter, it was obvious to a person of ordinary skill in the art to combine Asano with a pivot-mounted pedal position sensor. There then was a marketplace creating a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for doing so. The Federal Circuit considered the issue too narrowly by, in effect, asking whether a pedal designer writing on a blank slate would have chosen both Asano and a modular sensor similar to the ones used in the Chevrolet trucks and [***714] disclosed in the *'068 patent*. The proper question was whether a pedal designer of ordinary skill in the art, facing the wide range of needs created by developments in the field, would have seen an obvious benefit to upgrading Asano with a sensor. For such a designer starting with Asano, the question was where to attach the sensor. The *'936 patent* taught the utility of putting the sensor on the pedal device. Smith, in turn, explained not to put the sensor on the pedal footpad, but instead on the structure. And from Rixon's known wire-chafing problems, and Smith's teaching that the pedal assemblies must not precipitate any motion in the connecting wires, the designer would know to place the sensor on a nonmoving part of the pedal structure. The most obvious such point is a pivot point. The designer, accordingly, would follow Smith in mounting the sensor there. Just as it was possible to begin with the objective to upgrade Asano to work with a computer-controlled throttle, so too was it possible to take an adjustable electronic pedal like Rixon and seek an improvement that would avoid the wire-chafing problem. Teleflex has not shown anything in the prior art that taught away from the use of Asano, nor any secondary factors to dislodge the determination that claim 4 is obvious. Pp. 20-23.

3. The Court disagrees with the Federal Circuit's holding that genuine issues of material fact precluded summary judgment. The ultimate judgment of obviousness is a legal determination. *Graham, 383 U.S., at 17, 86 S. Ct. 684, 15 L. Ed. 2d 545*. Where, as here, the prior art's content, the patent claim's scope, and the level of ordinary skill in the art are not in material dispute and the claim's obviousness is apparent, summary judgment is appropriate. P. 23.

119 Fed. Appx. 282, reversed and remanded.

COUNSEL: James W. Dabney argued the cause for petitioner.

Thomas G. Hungar argued the cause for the United States, as amicus curiae, by special leave of court.

Thomas C. Goldstein argued the cause for respondents.

JUDGES: Kennedy, J., delivered the opinion for a unanimous Court.

OPINION BY: KENNEDY

OPINION

[*405] [**1734] Justice **Kennedy** delivered the opinion of the Court.

Teleflex Incorporated and its subsidiary Technology Holding Company--both referred to here as Teleflex--sued KSR International Company for patent infringement. The patent at issue, *United States Patent No. 6,237,565* B1, is entitled "Adjustable [*406] Pedal Assembly With Electronic Throttle Control." Supp. App. 1. The patentee is Steven J. Engelgau, and the patent is referred to as "the Engelgau patent." Teleflex holds the exclusive license to the patent.

Claim 4 of the Engelgau patent describes a mechanism for combining an electronic sensor with an adjustable automobile pedal so the pedal's position can be transmitted to a computer that controls the throttle in the vehicle's engine. When Teleflex accused KSR of infringing the Engelgau patent by adding an electronic sensor to one of KSR's previously designed pedals, KSR countered that claim 4 was invalid under the Patent Act, *35 U.S.C. § 103 (2000ed. and Supp. IV)*, because its subject matter was obvious.

[HN1] [***LEdHR1] [1]*Section 103(a)* forbids issuance of a patent when "the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having [***715] ordinary skill in the art to which said subject matter pertains."

In *Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 86 S. Ct. 684, 15 L. Ed. 2d 545 (1966)*, the Court set out a framework for applying the statutory language of *§ 103*, language itself based on the logic of the earlier

decision in *Hotchkiss v. Greenwood, 52 U.S. 248, 11 How. 248, 13 L. Ed. 683 (1851)*, and its progeny. See *383 U.S., at 15-17, 86 S. Ct. 684, 15 L. Ed. 2d 545*. The analysis is objective:

> [HN2] [***LEdHR2] [2]"Under *§ 103*, the scope and content of the prior art are to be determined; differences between the prior art and the claims at issue are to be ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, failure of others, etc., might be utilized to give light to the circumstances surrounding the origin of the subject matter sought to be patented." *Id., at 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545*.

[*407] While the sequence of these questions might be reordered in any particular case, the factors continue to define the inquiry that controls. If a court, or patent examiner, conducts this analysis and concludes the claimed subject matter was obvious, the claim is invalid under *§ 103*.

Seeking to resolve the question of obviousness with more uniformity and consistency, the Court of Appeals for the Federal Circuit has employed an approach referred to by the parties as the "teaching, suggestion, or motivation" test (TSM test), under which a patent claim is only proved obvious if "some motivation or suggestion to combine the prior art teachings" can be found in the prior art, the nature of the problem, or the knowledge of a person having ordinary skill in the art. See, *e.g., Al-Site Corp. v. VSI Int'l, Inc., 174 F.3d 1308, 1323-1324 (CA Fed. 1999)*. KSR challenges that [**1735] test, or at least its application in this case. See *119 Fed. Appx. 282, 286-290 (CA Fed. 2005)*. Because the Court of Appeals addressed the question of obviousness in a manner contrary to *§ 103* and our precedents, we granted certiorari, *548 U.S. 902, 126 S. Ct. 2965, 165 L. Ed. 2d 949 (2006)*. We now reverse.

I

A

In car engines without computer-controlled throttles, the accelerator pedal interacts with the throttle via cable or other mechanical link. The pedal arm acts as a lever rotating around a pivot point. In a cable-actuated throttle control the rotation caused by pushing down the pedal pulls a cable, which in turn pulls open valves in the carburetor or fuel injection unit. The wider the valves open, the more fuel and air are released, causing combustion to increase and the car to accelerate. When the driver takes his foot off the pedal, the opposite occurs as the cable is released and the valves slide closed.

In the 1990's it became more common to install computers in cars to control engine operation. Computer-controlled [*408] throttles open and close valves in response to electronic signals, not through force transferred from the pedal by a mechanical link. Constant, delicate adjustments of air and fuel mixture are possible. The computer's rapid processing of factors beyond the pedal's position improves [***716] fuel efficiency and engine performance.

For a computer-controlled throttle to respond to a driver's operation of the car, the computer must know what is happening with the pedal. A cable or mechanical link does not suffice for this purpose; at some point, an electronic sensor is necessary to translate the mechanical operation into digital data the computer can understand.

Before discussing sensors further we turn to the mechanical design of the pedal itself. In the traditional design a pedal can be pushed down or released but cannot have its position in the footwell adjusted by sliding the pedal forward or back. As a result, a driver who wishes to be closer or farther from the pedal must either reposition himself in the driver's seat or move the seat in some way. In cars with deep footwells these are imperfect solutions for drivers of smaller stature. To solve the problem, inventors, beginning in the 1970's, designed pedals that could be adjusted to change their location in the footwell. Important for this case are two adjustable pedals disclosed in *U.S. Patent Nos. 5,010,782* (filed July 28, 1989) (Asano) and *5,460,061* (filed Sept. 17, 1993) (Redding). The Asano patent reveals a support structure that houses the pedal so that even when the pedal location is adjusted relative to the driver, one of the pedal's pivot points stays fixed. The pedal is also designed so that the force necessary to push the pedal down is the same regardless of adjustments to its location. The Redding patent reveals a different, sliding mechanism where both

the pedal and the pivot point are adjusted.

We return to sensors. Well before Engelgau applied for his challenged patent, some inventors had obtained patents involving electronic pedal sensors for computer-controlled [*409] throttles. These inventions, such as the device disclosed in *U.S. Patent No. 5,241,936* (filed Sept. 9, 1991) ('936), taught that it was preferable to detect the pedal's position in the pedal assembly, not in the engine. The *'936 patent* disclosed a pedal with an electronic sensor on a pivot point in the pedal assembly. *U.S. Patent No. 5,063,811* (filed July 9, 1990) (Smith) taught that to prevent the [**1736] wires connecting the sensor to the computer from chafing and wearing out, and to avoid grime and damage from the driver's foot, the sensor should be put on a fixed part of the pedal assembly rather than in or on the pedal's footpad.

In addition to patents for pedals with integrated sensors inventors obtained patents for self-contained modular sensors. A modular sensor is designed independently of a given pedal so that it can be taken off the shelf and attached to mechanical pedals of various sorts, enabling the pedals to be used in automobiles with computer-controlled throttles. One such sensor was disclosed in *U.S. Patent No. 5,385,068* (filed Dec. 18, 1992) ('068). In 1994, Chevrolet manufactured a line of trucks using modular sensors "attached to the pedal assembly support bracket, adjacent to the pedal and engaged with the pivot shaft about which the pedal rotates in operation." *298 F. Supp. 2d 581, 589 (ED Mich. 2003)*.

The prior art contained patents involving the placement of sensors on adjustable pedals as well. For example, *U.S. Patent No. 5,819,593* (filed Aug. 17, 1995) (Rixon) discloses an adjustable pedal assembly with an [***717] electronic sensor for detecting the pedal's position. In the Rixon pedal the sensor is located in the pedal footpad. The Rixon pedal was known to suffer from wire chafing when the pedal was depressed and released.

This short account of pedal and sensor technology leads to the instant case.

B

KSR, a Canadian company, manufactures and supplies auto parts, including pedal systems. Ford Motor Company hired [*410] KSR in 1998 to supply an adjustable pedal system for various lines of automobiles with cable-actuated throttle controls. KSR developed an adjustable mechanical pedal for Ford and obtained *U.S. Patent No. 6,151,986* (filed July 16, 1999) ('986) for the design. In 2000, KSR was chosen by General Motors Corporation (GMC or GM) to supply adjustable pedal systems for Chevrolet and GMC light trucks that used engines with computer-controlled throttles. To make the *'986* pedal compatible with the trucks, KSR merely took that design and added a modular sensor.

Teleflex is a rival to KSR in the design and manufacture of adjustable pedals. As noted, it is the exclusive licensee of the Engelgau patent. Engelgau filed the patent application on August 22, 2000, as a continuation of a previous application for *U.S. Patent No. 6,109,241*, which was filed on January 26, 1999. He has sworn he invented the patent's subject matter on February 14, 1998. The Engelgau patent discloses an adjustable electronic pedal described in the specification as a "simplified vehicle control pedal assembly that is less expensive, and which uses fewer parts and is easier to package within the vehicle." Engelgau, col. 2, ll. 2-5, Supp. App. 6. Claim 4 of the patent, at issue here, describes:

> "A vehicle control pedal apparatus comprising:
>
> "a support adapted to be mounted to a vehicle structure;
>
> "an adjustable pedal assembly having a pedal arm moveable in for[e] and aft directions with "respect to said support;
>
> "a pivot for pivotally supporting said adjustable pedal assembly with respect to said support and defining a pivot axis; and
>
> "an electronic control attached to said support for controlling a vehicle system;
>
> "said apparatus characterized by said electronic control being responsive to said pivot for providing a signal that corresponds to pedal arm position as said pedal arm pivots [*411] about said pivot [**1737] axis between rest and applied positions wherein the position of said pivot remains constant while said pedal arm moves in fore and aft directions with

respect to said pivot." *Id.,* col. 6, ll. 17-36, Supp. App. 8 (diagram numbers omitted).

We agree with the District Court that the claim discloses "a position-adjustable pedal assembly with an electronic pedal position sensor attached to the support member of the pedal assembly. Attaching the sensor to the support member allows the sensor to remain in a fixed position while the driver adjusts the pedal." *298 F. Supp. 2d, at 586-587.*

Before issuing the Engelgau patent the U. S. Patent and Trademark Office (PTO) rejected one of the patent claims that was similar to, but [***718] broader than, the present claim 4. The claim did not include the requirement that the sensor be placed on a fixed pivot point. The PTO concluded the claim was an obvious combination of the prior art disclosed in Redding and Smith, explaining:

> "'Since the prior ar[t] references are from the field of endeavor, the purpose disclosed . . . would have been recognized in the pertinent art of Redding. Therefore it would have been obvious . . . to provide the device of Redding with the . . . means attached to a support member as taught by Smith.'" *Id., at 595.*

In other words Redding provided an example of an adjustable pedal and Smith explained how to mount a sensor on a pedal's support structure, and the rejected patent claim merely put these two teachings together.

Although the broader claim was rejected, claim 4 was later allowed because it included the limitation of a fixed pivot point, which distinguished the design from Redding's. *Ibid.* Engelgau had not included Asano among the prior art references, and Asano was not mentioned in the patent's prosecution. Thus, the PTO did not have before it an adjustable [*412] pedal with a fixed pivot point. The patent issued on May 29, 2001, and was assigned to Teleflex.

Upon learning of KSR's design for GM, Teleflex sent a warning letter informing KSR that its proposal would violate the Engelgau patent. "'Teleflex believes that any supplier of a product that combines an adjustable pedal with an electronic throttle control necessarily employs technology covered by one or more'" of Teleflex's patents. *Id., at 585.* KSR refused to enter a royalty arrangement with Teleflex; so Teleflex sued for infringement, asserting KSR's pedal infringed the Engelgau patent and two other patents. *Ibid.* Teleflex later abandoned its claims regarding the other patents and dedicated the patents to the public. The remaining contention was that KSR's pedal system for GM infringed claim 4 of the Engelgau patent. Teleflex has not argued that the other three claims of the patent are infringed by KSR's pedal, nor has Teleflex argued that the mechanical adjustable pedal designed by KSR for Ford infringed any of its patents.

C

The District Court granted summary judgment in KSR's favor. After reviewing the pertinent history of pedal design, the scope of the Engelgau patent, and the relevant prior art, the court considered the validity of the contested claim. [HN3] [***LEdHR3] [3] By direction of *35 U.S.C. § 282*, an issued patent is presumed valid. The District Court applied *Graham*'s framework to determine whether under summary-judgment standards KSR had overcome the presumption and demonstrated that claim 4 was obvious in light of the prior art in existence when [**1738] the claimed subject matter was invented. See *§ 103(a).*

The District Court determined, in light of the expert testimony and the parties' stipulations, that the level of ordinary skill in pedal design was "'an undergraduate degree in mechanical engineering (or an equivalent amount of industry experience) [and] familiarity with pedal control systems for [*413] vehicles.'" *298 F. Supp. 2d, at 590.* The court then set forth the relevant prior art, including the patents and pedal designs described above.

[***719] Following *Graham*'s direction, the court compared the teachings of the prior art to the claims of Engelgau. It found "little difference." *298 F. Supp. 2d, at 590.* Asano taught everything contained in claim 4 except the use of a sensor to detect the pedal's position and transmit it to the computer controlling the throttle. That additional aspect was revealed in sources such as the *'068 patent* and the sensors used by Chevrolet.

Under the controlling cases from the Court of Appeals for the Federal Circuit, however, the District Court was not permitted to stop there. The court was

required also to apply the TSM test. The District Court held KSR had satisfied the test. It reasoned (1) the state of the industry would lead inevitably to combinations of electronic sensors and adjustable pedals, (2) Rixon provided the basis for these developments, and (3) Smith taught a solution to the wire chafing problems in Rixon, namely, locating the sensor on the fixed structure of the pedal. This could lead to the combination of Asano, or a pedal like it, with a pedal position sensor.

The conclusion that the Engelgau design was obvious was supported, in the District Court's view, by the PTO's rejection of the broader version of claim 4. Had Engelgau included Asano in his patent application, it reasoned, the PTO would have found claim 4 to be an obvious combination of Asano and Smith, as it had found the broader version an obvious combination of Redding and Smith. As a final matter, the District Court held that the secondary factor of Teleflex's commercial success with pedals based on Engelgau's design did not alter its conclusion. The District Court granted summary judgment for KSR.

With principal reliance on the TSM test, the Court of Appeals reversed. It ruled the District Court had not been strict enough in applying the test, having failed to make [*414] "'finding[s] as to the specific understanding or principle within the knowledge of a skilled artisan that would have motivated one with no knowledge of [the] invention' . . . to attach an electronic control to the support bracket of the Asano assembly." *119 Fed. Appx., at 288* (brackets in original) (quoting *In re Kotzab, 217 F.3d 1365, 1371 (CA Fed. 2000))*. The Court of Appeals held that the District Court was incorrect that the nature of the problem to be solved satisfied this requirement because unless the "prior art references address[ed] the precise problem that the patentee was trying to solve," the problem would not motivate an inventor to look at those references. *119 Fed. Appx., at 288*.

Here, the Court of Appeals found, the Asano pedal was designed to solve the "'constant ratio problem'"--that is, to ensure that the force required to depress the pedal is the same no matter how the pedal is adjusted--whereas Engelgau sought to provide a simpler, smaller, cheaper adjustable electronic pedal. *Ibid.* As for Rixon, the court explained, that pedal suffered from the problem of wire chafing but was not designed to solve it. In the court's view Rixon did not teach anything helpful to Engelgau's purpose. Smith, in turn, did not relate to adjustable pedals and did not "necessarily go to the issue of motivation [**1739] to attach the electronic control on the support bracket of the pedal assembly." *Ibid.* When the patents were interpreted in this way, the Court of Appeals held, they would not have led a person of ordinary skill to put a sensor on the sort of pedal described in Asano.

[***720] That it might have been obvious to try the combination of Asano and a sensor was likewise irrelevant, in the court's view, because "'"[o]bvious to try" has long been held not to constitute obviousness.'" *Id., at 289* (quoting *In re Deuel, 51 F.3d 1552, 1559 (CA Fed. 1995))*.

The Court of Appeals also faulted the District Court's consideration of the PTO's rejection of the broader version of claim 4. The District Court's role, the Court of Appeals explained, was not to speculate regarding what the PTO might [*415] have done had the Engelgau patent mentioned Asano. Rather, the court held, the District Court was obliged first to presume that the issued patent was valid and then to render its own independent judgment of obviousness based on a review of the prior art. The fact that the PTO had rejected the broader version of claim 4, the Court of Appeals said, had no place in that analysis.

The Court of Appeals further held that genuine issues of material fact precluded summary judgment. Teleflex had proffered statements from one expert that claim 4 "'was a simple, elegant, and novel combination of features,'" *119 Fed. Appx., at 290*, compared to Rixon, and from another expert that claim 4 was nonobvious because, unlike in Rixon, the sensor was mounted on the support bracket rather than the pedal itself. This evidence, the court concluded, sufficed to require a trial.

II

A

We begin by rejecting the rigid approach of the Court of Appeals. Throughout this Court's engagement with the question of obviousness, our cases have set forth an expansive and flexible approach inconsistent with the way the Court of Appeals applied its TSM test here. To be sure, *Graham* recognized the need for "uniformity and definiteness." *383 U.S., at 18, 86 S. Ct. 684, 15 L. Ed. 2d 545*. Yet the principles laid down in *Graham* reaffirmed the "functional approach" of *Hotchkiss, 52 U.S. 248, 11 How. 248, 13 L. Ed. 683*. See *383 U.S., at 12, 86 S. Ct.*

684, 15 L. Ed. 2d 545. To this end, *Graham* set forth a broad inquiry and invited courts, where appropriate, to look at any secondary considerations that would prove instructive. *Id., at 17, 86 S. Ct. 684, 15 L. Ed. 2d 545*.

Neither the enactment of *§ 103* nor the analysis in *Graham* disturbed this Court's earlier instructions concerning the need for caution in granting a patent based on the combination of elements found in the prior art. For over a half century, the Court has held that [HN4] [***LEdHR4] [4] a "patent for a combination [*416] which only unites old elements with no change in their respective functions . . . obviously withdraws what already is known into the field of its monopoly and diminishes the resources available to skillful men." *Great Atlantic & Pacific Tea Co. v. Supermarket Equipment Corp., 340 U.S. 147, 152-153, 71 S. Ct. 127, 95 L. Ed. 162, 1951 Dec. Comm'r Pat. 572 (1950)*. This is a principal reason for declining to allow patents for what is obvious. The combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results. Three cases decided after *Graham* illustrate the application of this doctrine.

In *United States v. Adams, 383 U.S. 39, 40, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293 (1966)*, a companion case to *Graham*, the Court considered the obviousness of a "wet battery" that varied from [***721] prior designs in two ways: [**1740] It contained water, rather than the acids conventionally employed in storage batteries; and its electrodes were magnesium and cuprous chloride, rather than zinc and silver chloride. The Court recognized that when a patent claims a structure already known in the prior art that is altered by the mere substitution of one element for another known in the field, the combination must do more than yield a predictable result. *383 U.S., at 50-51, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293*It nevertheless rejected the Government's claim that Adams's battery was obvious. The Court relied upon the corollary principle that when the prior art teaches away from combining certain known elements, discovery of a successful means of combining them is more likely to be nonobvious. *Id., at 51-52, 86 S. Ct. 708, 15 L. Ed. 2d 572, 174 Ct. Cl. 1293*When Adams designed his battery, the prior art warned that risks were involved in using the types of electrodes he employed. The fact that the elements worked together in an unexpected and fruitful manner supported the conclusion that Adams's design was not obvious to those skilled in the art.

In *Anderson's-Black Rock, Inc. v. Pavement Salvage Co., 396 U.S. 57, 90 S. Ct. 305, 24 L. Ed. 2d 258 (1969)*, the Court elaborated on this approach. The subject matter of the patent before the Court was a device combining two pre-existing elements: a radiant-heat [*417] burner and a paving machine. The device, the Court concluded, did not create some new synergy: The radiant-heat burner functioned just as a burner was expected to function; and the paving machine did the same. The two in combination did no more than they would in separate, sequential operation. *Id., at 60-62, 90 S. Ct. 305, 24 L. Ed. 2d 258*. In those circumstances, "while the combination of old elements performed a useful function, it added nothing to the nature and quality of the radiant-heat burner already patented," and the patent failed under *§ 103*. *Id., at 62, 90 S. Ct. 305, 24 L. Ed. 2d 258* (footnote omitted).

Finally, in *Sakraida v. AG Pro, Inc., 425 U.S. 273, 96 S. Ct. 1532, 47 L. Ed. 2d 784 (1976)*, the Court derived from the precedents the conclusion that when a patent "simply arranges old elements with each performing the same function it had been known to perform" and yields no more than one would expect from such an arrangement, the combination is obvious. *Id., at 282, 96 S. Ct. 1532, 47 L .Ed. 2d 784*.

The principles underlying these cases are instructive when the question is whether a patent claiming the combination of elements of prior art is obvious. [HN5] [***LEdHR5] [5] When a work is available in one field of endeavor, design incentives and other market forces can prompt variations of it, either in the same field or a different one. If a person of ordinary skill can implement a predictable variation, *§ 103* likely bars its patentability. For the same reason, if a technique has been used to improve one device, and a person of ordinary skill in the art would recognize that it would improve similar devices in the same way, using the technique is obvious unless its actual application is beyond his or her skill. *Sakraida* and *Anderson's-Black Rock* are illustrative--a court must ask whether the improvement is more than the predictable use of prior art elements according to their established functions.

Following these principles may be [***722] more difficult in other cases than it is here because the claimed subject matter may involve more than the simple substitution of one known element for another or the mere application of a known technique to a piece of prior art ready for the improvement. [*418] Often, it will be

necessary for a court to look to interrelated teachings of multiple patents; the effects of demands known to the design community or present in the marketplace; and the background knowledge possessed by a person having [**1741] ordinary skill in the art, all in order to determine whether there was an apparent reason to combine the known elements in the fashion claimed by the patent at issue. To facilitate review, this analysis should be made explicit. See *In re Kahn, 441 F.3d 977, 988 (CA Fed. 2006)* ([HN6] [***LEdHR6] [6] "[R]ejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness"). As our precedents make clear, however, the analysis need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ.

B

When it first established the requirement of demonstrating a teaching, suggestion, or motivation to combine known elements in order to show that the combination is obvious, the Court of Customs and Patent Appeals captured a helpful insight. See *Application of Bergel, 292 F.2d 955, 956-957, 48 C.C.P.A. 1102, 1961 Dec. Comm'r Pat. 504 (1961)*. As is clear from cases such as *Adams*, [HN7] [***LEdHR7] [7] a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Although common sense directs one to look with care at a patent application that claims as innovation the combination of two known devices according to their established functions, it can be important to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. This is so because inventions in most, if not all, instances rely upon building blocks long since uncovered, and claimed discoveries almost of necessity [*419] will be combinations of what, in some sense, is already known.

Helpful insights, however, need not become rigid and mandatory formulas; and when it is so applied, the TSM test is incompatible with our precedents. [HN8] [***LEdHR8] [8] The obviousness analysis cannot be confined by a formalistic conception of the words teaching, suggestion, and motivation, or by overemphasis on the importance of published articles and the explicit content of issued patents. The diversity of inventive pursuits and of modern technology counsels against limiting the analysis in this way. In many fields it may be that there is little discussion of obvious techniques or combinations, and it often may be the case that market demand, rather than scientific literature, will drive design trends. Granting patent protection to advances that would occur in the ordinary course without real innovation retards progress and may, in the case of patents combining previously known elements, deprive prior inventions of their value or utility.

In the years since the Court of Customs and Patent Appeals set forth the [***723] essence of the TSM test, the Court of Appeals no doubt has applied the test in accord with these principles in many cases. There is no necessary inconsistency between the idea underlying the TSM test and the *Graham* analysis. But when a court transforms the general principle into a rigid rule that limits the obviousness inquiry, as the Court of Appeals did here, it errs.

C

The flaws in the analysis of the Court of Appeals relate for the most part to the court's narrow conception of the obviousness inquiry reflected in its application of the TSM test. [HN9] [***LEdHR9] [9] In determining whether the subject matter of a patent claim is obvious, neither the particular motivation nor the avowed purpose of the [**1742] patentee controls. What matters is the objective reach of the claim. If the claim extends to what is obvious, it is invalid under *§ 103*. One of the ways [*420] in which a patent's subject matter can be proved obvious is by noting that there existed at the time of invention a known problem for which there was an obvious solution encompassed by the patent's claims.

The first error of the Court of Appeals in this case was to foreclose this reasoning by holding that courts and patent examiners should look only to the problem the patentee was trying to solve. *119 Fed. Appx., at 288*. The Court of Appeals failed to recognize that [HN10] [***LEdHR10] [10] the problem motivating the patentee may be only one of many addressed by the patent's subject matter. The question is not whether the combination was obvious to the patentee but whether the combination was obvious to a person with ordinary skill in the art. Under the correct analysis, any need or

problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed.

The second error of the Court of Appeals lay in its assumption that a person of ordinary skill attempting to solve a problem will be led only to those elements of prior art designed to solve the same problem. *Ibid.* The primary purpose of Asano was solving the constant ratio problem; so, the court concluded, an inventor considering how to put a sensor on an adjustable pedal would have no reason to consider putting it on the Asano pedal. *Ibid.* Common sense teaches, however, that familiar items may have obvious uses beyond their primary purposes, and in many cases a person of ordinary skill will be able to fit the teachings of multiple patents together like pieces of a puzzle. Regardless of Asano's primary purpose, the design provided an obvious example of an adjustable pedal with a fixed pivot point; and the prior art was replete with patents indicating that a fixed pivot point was an ideal mount for a sensor. The idea that a designer hoping to make an adjustable electronic pedal would ignore Asano because Asano was designed to solve the constant [*421] ratio problem makes little sense. A person of ordinary skill is also a person of ordinary creativity, not an automaton.

The same constricted analysis led the Court of Appeals to conclude, in error, that a patent claim cannot be proved obvious merely by showing that the combination of elements was "[o]bvious to try." *Id., at 289* (internal quotation marks omitted). [HN11] [***LEdHR11] [11] When there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable [***724] solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under *§ 103*.

The Court of Appeals, finally, drew the wrong conclusion from the risk of courts and patent examiners falling prey to hindsight bias. [HN12] [***LEdHR12] [12] A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning. See *Graham , 383 U.S., at 36, 86 S. Ct. 684, 15 L. Ed. 2d 545* (warning against a "temptation to read into the prior art the teachings of the invention in issue" and instructing courts to "'guard against slipping into use of hindsight'" (quoting *Monroe Auto Equip. Co. v. Heckethorn Mfg. & Supply Co., 332 F.2d 406, 412 (CA6 1964))*). Rigid preventative rules that deny factfinders recourse to common sense, however, are [**1743] neither necessary under our case law nor consistent with it.

We note the Court of Appeals has since elaborated a broader conception of the TSM test than was applied in the instant matter. See, *e.g., DyStar Textilfarben GmbH & Co. Deutschland KG v. C. H. Patrick Co., 464 F.3d 1356, 1367 (CA Fed. 2006)* ("Our suggestion test is in actuality quite flexible and not only permits, but *requires*, consideration of common knowledge and common sense"); *Alza Corp. v. Mylan Labs., Inc., 464 F.3d 1286, 1291 (2006)* ("There is flexibility in our obviousness jurisprudence because a motivation [*422] may be found *implicitly* in the prior art. We do not have a rigid test that requires an actual teaching to combine . . .)". Those decisions, of course, are not now before us and do not correct the errors of law made by the Court of Appeals in this case. The extent to which they may describe an analysis more consistent with our earlier precedents and our decision here is a matter for the Court of Appeals to consider in its future cases. What we hold is that the fundamental misunderstandings identified above led the Court of Appeals in this case to apply a test inconsistent with our patent law decisions.

III

When we apply the standards we have explained to the instant facts, claim 4 must be found obvious. We agree with and adopt the District Court's recitation of the relevant prior art and its determination of the level of ordinary skill in the field. As did the District Court, we see little difference between the teachings of Asano and Smith and the adjustable electronic pedal disclosed in claim 4 of the Engelgau patent. A person having ordinary skill in the art could have combined Asano with a pedal position sensor in a fashion encompassed by claim 4, and would have seen the benefits of doing so.

A

Teleflex argues in passing that the Asano pedal cannot be combined with a sensor in the manner described by claim 4 because of the design of Asano's

pivot mechanisms. See Brief for Respondents 48-49, and n 17. Therefore, Teleflex reasons, even if adding a sensor to Asano was obvious, that does not establish that claim 4 encompasses obvious subject matter. This argument was not, however, [***725] raised before the District Court. There Teleflex was content to assert only that the problem motivating the invention claimed by the Engelgau patent would not lead to the solution of combining Asano with a sensor. See Teleflex's Response to KSR's Motion [*423] for Summary Judgment of Invalidity in No. 02-74586 (ED Mich.), pp 18-20, App. 144a-146a. It is also unclear whether the current argument was raised before the Court of Appeals, where Teleflex advanced the nonspecific, conclusory contention that combining Asano with a sensor would not satisfy the limitations of claim 4. See Brief for Plaintiffs-Appellants in No. 04-1152 (CA Fed.), pp 42-44. Teleflex's own expert declarations, moreover, do not support the point Teleflex now raises. See Declaration of Clark J. Radcliffe, Ph.D., Supp. App. 204-207; Declaration of Timothy L. Andresen, *id.*, at 208-210. The only statement in either declaration that might bear on the argument is found in the Radcliffe declaration:

> "Asano . . . and the Rixon . . . are complex mechanical linkage-based devices that are expensive to produce and assemble and difficult to package. It is exactly these difficulties with prior art designs that [Engelgau] resolves. The use of an adjustable pedal with a single pivot reflecting pedal position combined with an electronic control mounted between the [**1744] support and the adjustment assembly at that pivot was a simple, elegant, and novel combination of features in the Engelgau'*565 patent*." *Id.*, at 206, P 16.

Read in the context of the declaration as a whole this is best interpreted to mean that Asano could not be used to solve "[t]he problem addressed by Engelgau'565[:] to provide a less expensive, more quickly assembled, and smaller package adjustable pedal assembly with electronic control." *Id.*, at 205, P 10.

The District Court found that combining Asano with a pivot-mounted pedal position sensor fell within the scope of claim 4. *298 F. Supp. 2d, at 592-593*. Given the significance of that finding to the District Court's judgment, it is apparent that Teleflex would have made clearer challenges to it if it intended to preserve this claim. In light of Teleflex's failure [*424] to raise the argument in a clear fashion, and the silence of the Court of Appeals on the issue, we take the District Court's conclusion on the point to be correct.

B

The District Court was correct to conclude that, as of the time Engelgau designed the subject matter in claim 4, it was obvious to a person of ordinary skill to combine Asano with a pivot-mounted pedal position sensor. There then existed a marketplace that created a strong incentive to convert mechanical pedals to electronic pedals, and the prior art taught a number of methods for achieving this advance. The Court of Appeals considered the issue too narrowly by, in effect, asking whether a pedal designer writing on a blank slate would have chosen both Asano and a modular sensor similar to the ones used in the Chevrolet truckline and disclosed in the *'068 patent*. The District Court employed this narrow inquiry as well, though it reached the correct result nevertheless. The proper question to have asked was whether a pedal designer of ordinary skill, facing the wide range of needs created by developments in the field of endeavor, [***726] would have seen a benefit to upgrading Asano with a sensor.

In automotive design, as in many other fields, the interaction of multiple components means that changing one component often requires the others to be modified as well. Technological developments made it clear that engines using computer-controlled throttles would become standard. As a result, designers might have decided to design new pedals from scratch; but they also would have had reason to make pre-existing pedals work with the new engines. Indeed, upgrading its own pre-existing model led KSR to design the pedal now accused of infringing the Engelgau patent.

For a designer starting with Asano, the question was where to attach the sensor. The consequent legal question, then, is whether a pedal designer of ordinary skill starting with Asano would have found it obvious to put the sensor on [*425] a fixed pivot point. The prior art discussed above leads us to the conclusion that attaching the sensor where both KSR and Engelgau put it would have been obvious to a person of ordinary skill.

The *'936 patent* taught the utility of putting the sensor on the pedal device, not in the engine. Smith, in turn, explained to put the sensor not on the pedal's footpad but instead on its support structure. And from the known wire-chafing problems of Rixon, and Smith's teaching that "the pedal assemblies must not precipitate any motion in the connecting wires," Smith, col. 1, ll. 35-37, Supp. App. 274, the designer would know to place the sensor on a nonmoving part of the pedal structure. The most obvious nonmoving point on the structure from which a sensor can [**1745] easily detect the pedal's position is a pivot point. The designer, accordingly, would follow Smith in mounting the sensor on a pivot, thereby designing an adjustable electronic pedal covered by claim 4.

Just as it was possible to begin with the objective to upgrade Asano to work with a computer-controlled throttle, so too was it possible to take an adjustable electronic pedal like Rixon and seek an improvement that would avoid the wire-chafing problem. Following similar steps to those just explained, a designer would learn from Smith to avoid sensor movement and would come, thereby, to Asano because Asano disclosed an adjustable pedal with a fixed pivot.

Teleflex indirectly argues that the prior art taught away from attaching a sensor to Asano because Asano in its view is bulky, complex, and expensive. The only evidence Teleflex marshals in support of this argument, however, is the Radcliffe declaration, which merely indicates that Asano would not have solved Engelgau's goal of making a small, simple, and inexpensive pedal. What the declaration does not indicate is that Asano was somehow so flawed that there was no reason to upgrade it, or pedals like it, to be compatible with modern engines. Indeed, Teleflex's own declarations [*426] refute this conclusion. Dr. Radcliffe states that Rixon suffered from the same bulk and complexity as did Asano. See *id.,* at 206. Teleflex's other expert, however, explained that Rixon was itself designed by adding a sensor to a pre-existing mechanical pedal. See *id.,* at 209. If Rixon's base pedal was not too flawed to upgrade, then Dr. Radcliffe's declaration does not show Asano was either. Teleflex may have made a plausible argument that Asano is inefficient as compared [***727] to Engelgau's preferred embodiment, but to judge Asano against Engelgau would be to engage in the very hindsight bias Teleflex rightly urges must be avoided. Accordingly, Teleflex has not shown anything in the prior art that taught away from the use of Asano.

Like the District Court, finally, we conclude Teleflex has shown no secondary factors to dislodge the determination that claim 4 is obvious. Proper application of *Graham* and our other precedents to these facts therefore leads to the conclusion that claim 4 encompassed obvious subject matter. As a result, the claim fails to meet the requirement of *§ 103.*

We need not reach the question whether the failure to disclose Asano during the prosecution of Engelgau voids the presumption of validity given to issued patents, for claim 4 is obvious despite the presumption. We nevertheless think it appropriate to note that the rationale underlying the presumption--that the PTO, in its expertise, has approved the claim--seems much diminished here.

IV

A separate ground the Court of Appeals gave for reversing the order for summary judgment was the existence of a dispute over an issue of material fact. We disagree with the Court of Appeals on this point as well. To the extent the court understood the *Graham* approach to exclude the possibility of summary judgment when an expert provides a conclusory affidavit addressing the question of obviousness, it misunderstood the role expert testimony plays in the analysis. [HN13] [***LEdHR13] [13] [*427] In considering summary judgment on that question the district court can and should take into account expert testimony, which may resolve or keep open certain questions of fact. That is not the end of the issue, however. The ultimate judgment of obviousness is a legal determination. *Graham, 383 U.S., at 17, 86 S. Ct. 684, 15 L. Ed. 2d 545.* Where, as here, the content of the prior art, the scope of the patent [**1746] claim, and the level of ordinary skill in the art are not in material dispute, and the obviousness of the claim is apparent in light of these factors, summary judgment is appropriate. Nothing in the declarations proffered by Teleflex prevented the District Court from reaching the careful conclusions underlying its order for summary judgment in this case.

* * *

We build and create by bringing to the tangible and palpable reality around us new works based on instinct,

simple logic, ordinary inferences, extraordinary ideas, and sometimes even genius. These advances, once part of our shared knowledge, define a new threshold from which innovation starts once more. And [HN14] [***LEdHR14] [14] as progress beginning from higher levels of achievement is expected in the normal course, the results of ordinary innovation are not the subject of exclusive rights under the patent laws. Were it otherwise patents might stifle, rather than promote, the progress of useful arts. See *U.S. Const., Art. I, § 8, cl. 8*. These premises led to the bar on patents claiming obvious subject matter established in *Hotchkiss* and codified in *§ 103*. Application of the bar must not be confined within a test or formulation too constrained to serve its purpose.

KSR provided convincing evidence that mounting a modular sensor on a fixed pivot point of the Asano pedal was a design step well within the [***728] grasp of a person of ordinary skill in the relevant art. Its arguments, and the record, demonstrate that claim 4 of the Engelgau patent is obvious. In rejecting the District Court's rulings, the Court of Appeals [*428] analyzed the issue in a narrow, rigid manner inconsistent with *§ 103* and our precedents. The judgment of the Court of Appeals is reversed, and the case is remanded for further proceedings consistent with this opinion.

It is so ordered.

REFERENCES
35 U.S.C.S. § 103

Chisum on Patents §§ 5.02-5.04, 11.06 (Matthew Bender)

L Ed Digest, Patents § 19.1

L Ed Index, Patents

Supreme Court's views as to what is patentable subject matter under federal law as "process," "machine," "manufacture," or "composition of matter." *65 L. Ed. 2d 1197*.

OPM has not previously intervened provides this court with the benefits of the Board's review of the petition only if the Board considers the petition on the merits. The portion of section 7703(d) granting OPM the right to seek reconsideration by the Board would be emasculated if the Board may refuse reconsideration without addressing the merits of the substantive issues raised by OPM.

The legislative history of section 7703(d) lends support to our interpretation. The Senate Report states that the Board's reconsideration of its decision in light of OPM's concerns may "avoid unnecessary appeals by the Director." S.Rep. No. 95-969, 95th Cong.2d Sess. 64, *reprinted in* 1978 U.S.Code and Admin.News 2723, 2786. The Board's interpretation would not avoid unnecessary appeals by the Director. On the contrary, the Board's erroneous interpretation necessitates a preliminary appeal by OPM, as it has in this case, in order to overturn a Board decision that the Director's exercise of discretion was not proper followed by a remand and a second appeal respecting the merits.

Conclusion

We conclude, as a matter of interpretation of the statute, that when the Director seeks reconsideration of a decision of the Merit Systems Protection Board, the Board may not refuse to consider the Director's petition on the merits because it disagrees with the Director's discretionary determinations which the Director is required to make before filing the petition. Accordingly, we vacate the decision of the Board and remand for it to consider the merits of the Director's petition.

Costs

Each party shall bear its own costs.

VACATED AND REMANDED

In re Achim M. KULLING and Helmut H. Steinhausen.

No. 89-1516.

United States Court of Appeals, Federal Circuit.

March 8, 1990.

Patent applicant appealed decision of the United States Patent and Trademark Office Board of Patent Appeals and Interferences, which rejected claims in patent application. The Court of Appeals, Archer, Circuit Judge, held that patent application for process of recovering sulfuric acid used in production of titanium dioxide was properly rejected on grounds of obviousness.

Affirmed.

Patents ⇐16.25

Patent application for process of recovering sulfuric acid used in production of titanium dioxide was properly rejected on grounds of obviousness; any factual shortcomings in prior patent for similar process were sufficiently bridged by secondary references. 35 U.S.C.A. § 103.

Robert G. Mukai, Burns, Doane, Swecker & Mathis, of Alexandria, Va., argued, for appellant.

Harris A. Pitlick, Associate Sol., Office of the Sol., of Arlington, Va., argued for appellee. With him on the brief was Fred E. McKelvey, Sol.

Before NIES, Circuit Judge, BENNETT, Senior Circuit Judge, and ARCHER, Circuit Judge.

ARCHER, Circuit Judge.

Achim M. Kulling and Helmut H. Steinhausen (Kulling) appeal the decision of the United States Patent Office (PTO) Board of Patent Appeals & Interferences (Board) affirming the examiner's rejection under 35 U.S.C. § 103 (1982 & Supp. II 1984) of all

24 claims of their patent application. We affirm.

Background

Claim 1 [1] of Kulling's patent application is directed to a process for the treatment of a dilute iron (II) sulfate-containing sulfuric acid solution resulting from the hydrolysis of a titanyl sulfate solution in the production of titanium dioxide. The process is intended to achieve a high recovery of sulfuric acid while minimizing the amount of recovered contaminants (metal sulfates, chromium and vanadium) so that acid may be recycled for further titanium dioxide production.

The treatment process is basically comprised of five steps:

(a) concentrating the dilute iron (II) sulfate-containing sulfuric acid solution to obtain a suspension of the precipitated metal sulfate in sulfuric acid;

(b) centrifuging the suspension in a screen centrifuge to separate the precipitated sulfates from the acid solution;

(c) pre-washing the retained solids with 2 to 4% by volume of the feed solution to step (a) with respect to the volume of the original suspension;

(d) washing the retained solids with 1 to 2% by volume of water with respect to the volume of the original suspension; and

(e) recycling the filtrates of washing steps (c) and (d) either for use in the production of titanium dioxide and/or the solution treatment process.

The examiner rejected Kulling's claims on the basis of Christensen, United States Patent No. 2,001,409, in view of any one of several secondary references. In his Examiner's Answer, the examiner described Christensen as follows:

> Christensen discloses the treatment of liquors from the production of TiO_2 from ilmenite ores starting on page 8 column 1, line 53 to page 9 column 1, lines [sic] 38 which is discussed inconjunction [sic] with his figure 6. In this process the acidic iron sulfate solution formed by the hydrolysis in 35 and separated in 37 is supplied to concentrator 38 where it is concentrated to form ferrous sulfate slurried in 60% acid. This 60% slurry is then separated into a filtrate and a cake in 39 and 40. A portion of the separated 60% acid from 39 or 40 may be returned to the concentrator to secure a fluid pulp which can be efficiently handled by the apparatus. The cake is washed on item 40 to remove residual acid on the cake using a combination of iron sulfate containing solutions and wash liquor. Christensen page 5 column 2, lines 15-20 states that item 40 can be either a filter or a centrifuge and washing can be done in both types of apparatus.
>
> Accordingly Christensen fairly shows the overall combination of the instant claims to include the concentration of the same feed solution, separation by centrifuging of the solids from the concentrated solution, washing of the separated solids using a plural wash, and recycle of the filtrates from the centrifuging to the concentrator which is part of the treatment of the solution and also recycle of the separated concentrated acid to the production of titanium dioxide.
>
> Christensen does not show the specific use of a portion of the feed liquor to the concentrator to wash the filter cake although one of the wash liquors used by Christensen is an [sic] ferrous sulfate solution as is the feed solution to the concentrator. Christensen also does not specifically recite the numerical quantities of wash liquors used in the instant claims.

Notwithstanding these deficiencies of Christensen's disclosure, the examiner concluded that the claimed invention would have been obvious to one of skill in the art because the secondary references, Miller (U.S. Patent No. 3,273,959), Arnold, et al. (U.S. Patent No. 4,291,002), Hellmers, et al. (U.S. Patent No. 3,260,567), and Pike (U.S. Patent No. 2,798,790), disclosed the "use of a portion of the feed solution to wash the centrifuge cake" and because:

1. Since Kulling has not separately argued the merits of dependent claims 2-24, they stand or fall with independent claim 1. *In re Kaslow*, 707 F.2d 1366, 1376 (Fed. Cir.1983).

[t]he determination of the precise amount [of] wash solution and water used in the wash is a matter of routine optimization obvious to one of ordinary skill in the art balancing normal considerations of the purity of the washed cake required, the loss of cake via dissolution into the wash liquor. Increased washing increases the purity of the cake, the amount of wash liquors required, the amount of cake dissolved and the quantity of spent wash liquor to be processed.

On appeal, the Board affirmed the examiner and, in doing so, adopted the reasoning expressed in his Answer.

OPINION

The issue in this appeal is whether the Board erred in holding that claims 1–24 of Kulling's patent application were unpatentable under 35 U.S.C. § 103. Although an obviousness determination *per se* is a question of law which we review *de novo*, it is based upon underlying factual inquiries concerning the claimed invention and the prior art, which predicate findings are binding on this court unless shown to be clearly erroneous. *See In re Caveney*, 761 F.2d 671, 674 (Fed.Cir.1985).

We have reviewed the examiner's analysis and findings with respect to the prior art which the Board adopted and are unpersuaded that those findings are clearly erroneous. Further, we agree that they lead to the conclusion that Kulling's claimed process would have been obvious to one skilled in the art.

The Board determined that the teachings of the secondary references would have motivated the skilled artisan to use the concentrator feed solution as the pre-wash eluent in the process disclosed by Christensen. Its conclusion was based on the similarity between these two solutions in the Christensen process and the teaching of the secondary art wherein the feed solution is also used as an eluent. We find no error in the Board's finding that the secondary references, despite their relation to other specific but analogous chemical processes, provide an ample suggestion to bridge any factual "shortcoming" of Christensen. It is admitted by Kulling that in the Miller process the trona feed solution is also utilized as the eluent in the wash sequence. Although Miller's specific process is designed to recover the contents of the filter cake rather than the filtrate, it clearly suggests that when the wash solution is equivalent to an earlier existing solution, the latter may be used as a source for the former. The teaching of Miller is sufficient to support the Board's conclusion.

In addition, the Board found that the amount of eluent to be used in the washing sequence was a matter of routine optimization in the pertinent art. Kulling has not shown this finding to be clearly erroneous and, further, it is fully supported by Christensen's disclosure concerning the need to avoid undue amounts of wash solution. While this discussion is in relation to Christensen's ore treatment process, it is apparent that Christensen discloses that the wash sequence for the solution treatment process could be the same. Indeed, in describing the wash treatment for Fig. 4, Christensen expressly refers to his earlier discussion of the Fig. 3 wash sequence. *See* page 6, col. 1, line 58—col. 2, line 30 ("as previously described").

Kulling argues the claims are patentable because only minimal amounts of chromium and vanadium are extracted from the filter cake when the wash volumes are limited as set forth in claim 1. However, "objective evidence of nonobviousness must be commensurate in scope with the claims." *In re Lindner*, 457 F.2d 506, 508 (CCPA 1972). Here, the rejected claims read on a process for treating solutions which contain neither chromium nor vanadium as there is no indication, either in the claims, in the specification, or otherwise, that either chromium or vanadium is or must be present in the dilute iron (II) sulfate-containing sulfuric acid solution to which the claimed process is directed. Accordingly, as the Board correctly noted, Kulling cannot rely upon the minimal extraction of chromium or vanadium as an unexpected benefit to support the patentability of his claims.

Although Kulling argues to the contrary, the Board adopted the examiner's finding

that Christensen suggests the use of a "screen centrifuge" as the separating apparatus that may be used to separate the precipitated sulfates and the acid filtrate. We have reviewed the Christensen disclosure and conclude that the Board's finding is not clearly erroneous. Although Christensen's "centrifugal filter of proper design" is referred to in connection with the ore treatment process, a centrifuging apparatus is disclosed as useful in the treatment of sulfuric acid solutions as well. *See* page 6, col. 1, lines 58–65.

Kulling's other challenges to the Board's decision, all of which we have considered, fall short of establishing error on the part of the Board. In the absence of evidence of nonobviousness, we agree that Kulling's process would have been obvious to the skilled artisan and, accordingly, the Board's decision is

AFFIRMED.

59 CCPA

Application of Paul L. LINDNER.

Patent Appeal No. 8634.

United States Court of Customs and Patent Appeals.

April 6, 1972.

Proceeding in matter of an application for a patent. The Board of Appeals of United States Patent Office, Serial No. 400,901, affirmed decision of the primary examiner finally rejecting as unpatentable all of the involved claims, and the applicant appealed. The Court of Customs and Patent Appeals, Almond, J., held that claims of application for asserted invention relating to dispersant compositions which are particularly useful in emulsifying water-insoluble organic solvent solutions of biocidal toxicant (i. e., insecticide, weed killer, herbicide, or soil fumigant) and aqueous solutions of fertilizer material were properly rejected as having been anticipated by prior art.

Affirmed.

1. Patents ⇐66(1.12)

Claims of application for asserted invention relating to dispersant compositions which are particularly useful in emulsifying water-insoluble organic solvent solutions of biocidal toxicant (i. e., insecticide, weed killer, herbicide, or soil fumigant) and aqueous solutions of fertilizer material were properly rejected as having been anticipated by prior art. 35 U.S.C.A. § 103.

2. Patents ⇐18

Objective evidence of nonobviousness must be commensurate in scope with the claims.

3. Patents ⇐112(1)

Mere conclusory statements in specification and affidavits are entitled to little weight when the Patent Office questions the efficacy of those statements. Patent Office Practice Rules, rule 132, 35 U.S.C.A. App.

Sidney Wallenstein, Chicago, Ill. (Wallenstein, Spangenberg, Hattis & Strampel, Chicago, Ill.), attys. of record, for appellant; Samuel Stearman, Washington, D. C., of counsel.

S. Wm. Cochran, Washington, D. C., for the Commissioner of Patents; Jack E. Armore, Washington, D. C., of counsel.

Before RICH, ALMOND, BALDWIN and LANE, Judges, and MALETZ, Judge, United States Customs Court, sitting by designation.

ALMOND, Judge.

This is an appeal from the decision of the Patent Office Board of Appeals affirming the rejection of claims 1, 2, 5, 6, 8, 10, 11, 13, 15, 17, and 19 in appellant's application entitled "Dispersant Compositions Comprising (A) Phosphoric Esters of Ethoxylated Long Chain Compounds and (B) Surfactant Polybasic Compounds Containing at Least One Sulfonic or Sulfuric Acid Radical." [1] No claims have been allowed.

The invention relates to dispersant compositions which are particularly useful in emulsifying water-insoluble organic solvent solutions of biocidal toxicant (i. e., insecticide, weed killer, herbicide, or soil fumigant) and aqueous solutions of fertilizer material. Appellant states in his specification that while a number of dispersant compositions are known which produce excellent dispersions of biocidal toxicants in aqueous solutions of a wide variety of water-soluble fertilizers, there are some fertilizer solutions (for example, liquid fertilizers commonly referred to as 7–21–7 and 6–18–6) which are particularly resistant or refractory to the production of fully satisfactory dispersions. The claimed dispersant compositions comprise ingredients (a) and (b) which are said to "coact to produce a synergistic effect" in that they produce stable dispersions with refractory fertilizer solutions as well as other fertilizer solutions. The compounds which may be used as ingre-

1. Serial No. 400,901 filed October 1, 1964.

dient (a) are water-soluble to readily water-dispersible phosphoric acid mono- and di- esters of polyoxyethylene ethers, usually in the form of ethylene oxide adducts, of long chain aliphatic alcohols, long chain aliphatic mercaptans and alkyl phenols. The compounds which may be used as ingredient (b) are organic solvent-soluble surfactant polybasic acids which contain at least one radical selected from the group consisting of sulfonic acid and sulfuric acid radicals.

Claim 1 is illustrative:

1. A dispersant composition comprising (a) a water-soluble to readily water-dispersible phosphoric acid ester of at least one member selected from the group consisting of (1) long chain aliphatic ethers and thioethers of polyoxyethylene glycols, the long chain aliphatic radicals containing from 10 to 26 carbon atoms, and (2) polyoxyethylene glycol ethers of alkylated phenols the alkyl radical or radicals of which contain a total of from 7 to 24 carbon atoms, the number of oxyethylene groups in the molecules of said (a) compounds falling within the range of 4 to 30, and (b) an organic solvent-soluble surfactant polybasic acid compound containing at least one radical selected from the group consisting of sulfonic and sulfuric acid radicals.

Like claim 1, claims 2, 5, 6, 8, 10 and 11 are directed to dispersant compositions. The recitation of the composition of ingredients (a) and (b) varies in breadth in these claims. Claims 13 and 15 are directed to toxicant concentrate containing a dispersant composition. Claims 17 and 19 are for a combination of biocidal toxicant water-soluble organic salt fertilizer composition emulsified with a dispersant composition. Appellant, in his brief, indicates that he considers claims 10, 11 and 17, as well as claim 1, to be illustrative. However, since all the claims have otherwise been considered together by both the Patent Office and appellant, they apparently will stand or fall together.

The references relied upon are:

Lindner	2,976,211	March 21, 1961
Nunn et al. (Nunn)	3,004,056	October 10, 1961

Lindner discloses dispersant compositions (as well as toxicant concentrates and dispersions comprising toxicants and aqueous solutions of water-soluble fertilizers) containing (a) certain polybasic acid compound surfactants and (b) certain amine salts of alkyl benzene sulfonic acids. Ingredient (a) of the mixture in the Lindner patent is the same as ingredient (b) of the claimed mixture.

Nunn discloses that phosphoric acid esters of various ethylene oxide adducts, the same compounds as those of ingredient (a) of the claimed mixture, may be used generally as dispersing agents.

[1] The examiner rejected all the claims under 35 U.S.C. § 103 as unpatentable over Lindner in view of Nunn, reasoning that since the compounds shown in Lindner and the compounds shown in Nunn are each known to be dispersants, it would have been obvious to combine these two old dispersants, and one of ordinary skill in the art would expect a mixture of such dispersants also to be a dispersant. The board agreed with the examiner.

We, too, agree with the examiner. The polybasic acid compounds of ingredient (b) and the phosphoric acid esters of ingredient (a) are all known dispersants as indicated by the art of record. In addition, Lindner indicates that mixtures of dispersant compositions may be advantageously used to permit combining concentrated aqueous fertilizer solutions with organic solvent solutions of biocidal substances to produce homogenous emulsions or dispersions. While the second ingredient in the mixture in the Lindner patent (i. e., the amine salts of alkyl benzene sulfonic acids) is in no way related to the second ingredient in the claimed mixtures (i. e., the phosphoric acid esters), this does not detract from the teaching in Lindner that mixtures of known dispersant compositions may be used. Considering the various teachings of the prior art, we

conclude that the suggested combination of the polybasic acids of Lindner with the phosphoric acid esters of Nunn would indeed have been prima facie obvious to those skilled in the art.

Although appellant elsewhere in his brief contends that there is no teaching which suggests combination of the ingredients of Lindner and Nunn (an argument which we reject for the reasons given above), at one point he seemingly admits that the Patent Office has established a case of prima facie obviousness when he states:

> If all that appellant obtained by combining the (a) and (b) classes of dispersants was simply a dispersant composition whose properties and utilities were essentially the same as those of the (a) and (b) dispersants *per se*, we should have no quarrel with the decision of the Board of Appeals * * *.

It is appellant's position that when the particular (a) and (b) classes of dispersants are used in combination, a synergistic effect is produced and properties are obtained and results are achieved which are unobtained and unobtainable with either the (a) or (b) dispersants alone. In support of this contention, appellant relies on both the specification as filed and a Rule 132 affidavit submitted in response to the examiner's continuance of the rejection "in the absence of convincing evidence of unexpected coaction."

The examiner and the board found the Rule 132 affidavit unpersuasive for a number of reasons, but basically it was their view that since only a single composition of those included in the claims was tested, the affidavit "falls far short of establishing that the compositions encompassed by claims of the scope of those on appeal possess unexpected properties." The same complaint about a lack of sufficient factual evidence of a synergistic effect with all the compositions claimed was leveled against the specification.

[2] We fully agree with the position of the Patent Office in that regard. It is well established that the objective evidence of nonobviousness must be commensurate in scope with the claims. *See, e. g.*, In re Hyson, 453 F.2d 764, 59 C.C.P.A. —— (1972); In re Tiffin, 448 F.2d 791, 58 C.C.P.A. 1420 (1971) (per curiam). Here only one mixture of ingredients was tested, that being a mixture of (a) phosphoric acid ester of 12 mol ethylene oxide adduct of nonyl phenol (containing about 60% mono- and about 17.5% di- ester) and (b) half ammonium half isopropylamine salt of the sulfosuccinic acid ester of the oleic acid amide of monoisopropanolamine (65% active). This particular mixture was found to produce a good dispersion with refractory 7-21-7 fertilizer solutions. As the board noted, the specification also indicates that the same mixture was successfully used with 7-21-7 fertilizer solutions. The claims, however, are much broader in scope, covering mixtures of numerous compounds, and we have to agree with the Patent Office that there is no "adequate basis for reasonably concluding that the great number and variety of compositions included by the claims would behave in the same manner as the [single] tested composition." *Cf.*, In re Saunders, 444 F. 2d 599, 605, 58 C.C.P.A. 1316, 1324 (1971).

[3] The affidavit and specification do contain allegations that synergistic results are obtained with all the claimed compositions, but those statements are not supported by any factual evidence other than that limited amount of evidence discussed above. This court has said previously that mere lawyers' arguments unsupported by factual evidence are insufficient to establish unexpected results. In re Cavanagh, 436 F.2d 491, 58 C.C.P.A. 856 (1971); In re Takai, 449 F.2d 1393, 59 C.C.P.A. —— (1971). Likewise, mere conclusory statements in the specification and affidavits are entitled to little weight when the Patent Office questions the efficacy of those statements. In re Hyson, supra; In re D'Ancicco, 452 F.2d 1060, 59 C.C.P.A. —— (1972). After considering the spec-

ification, affidavit, and arguments of counsel, we agree with the board that there is insufficient evidence to overcome the case of prima facie obviousness found to exist here.

The board also affirmed the examiner's rejection of all claims, except claim 11, under 35 U.S.C. § 112. However, because of our disposition of the rejection under 35 U.S.C. § 103, we find it unnecessary to reach the § 112 issue.

The decision of the board is affirmed.

Affirmed.

59 CCPA

Application of CLAIROL INCORPORATED.

Patent Appeal No. 8625.

United States Court of Customs and Patent Appeals.

April 6, 1972.

Applicant for registration of mark appealed from a decision of the Trademark Trial and Appeal Board, serial No. 254,510 sustaining a refusal to register the mark. The Court of Customs and Patent Appeals, Baldwin, J., held that mark SWEDISH CRYSTAL for a hair tinting, dyeing and coloring preparation was because of the arbitrariness of the mark as well as fact that it was always used in addition to a shade designation, suitable for registration.

Reversed.

1. Trade Regulation ⇐152

Mark may be used for both a trademark purpose and a nontrademark purpose and still be a valid trademark.

2. Trade Regulation ⇐155

Mark SWEDISH CRYSTAL for a hair tinting, dyeing and coloring preparation was, because of the arbitrariness of the mark as well as fact that it was always used in addition to a shade designation, suitable for registration.

Weil, Lee & Bergin, New York City, attorneys of record, for appellant. Alfred T. Lee, David J. Kera, New York City, of counsel.

S. Wm. Cochran, Washington, D. C., for the Commissioner of Patents. Fred W. Sherling, Washington, D. C., of counsel.

Before RICH, ALMOND, BALDWIN and LANE, Judges.

BALDWIN, Judge.

This appeal is from the decision of the Trademark Trial and Appeal Board sustaining a refusal to register the mark SWEDISH CRYSTAL for a hair tinting, dyeing and coloring preparation. The board's opinion appears at 161 USPQ 500 (1969). Familiarity with that opinion is assumed.

The basis for the refusal to register was that the mark was not used as a means for distinguishing the goods of others, but only as a color designation to identify the color "light muted ash." The specimen reproduced in the board's opinion shows a typical use of the mark, judging from the numerous other specimens of labels, advertisements, etc., submitted as exhibits by appellant. In all those exhibits, the mark appears in combination with the number "411" and the words "Light Muted Ash."

We agree with the dissenting opinion of board member Leach, reproduced here for convenience:

> "SWEDISH CRYSTAL" is a coined and completely arbitrary term which does not in itself have a connotation of color, and it is applied in the manner of a trademark to the containers for applicant's product. Such being the case, there is no reason to suppose that it does not serve to identify and distinguish applicant's goods from similar goods of others; and the fact that it may also serve to distinguish a

Drugs 13: 161-218 (1977)

Doxepin Up-to-Date: A Review of its Pharmacological Properties and Therapeutic Efficacy with Particular Reference to Depression

R.M. Pinder, R.N. Brogden, T.M. Speight and G.S. Avery

Australasian Drug Information Services, Auckland

Various sections of the manuscript reviewed by: *F.J. Ayd*, Baltimore, Md. USA; *T.A. Ban*, Tennessee Neuropsychiatric Institute, Nashville, Tenn. USA; *G. Bianchi*, Bardon West, Australia; *K.H. Boysen*, Vienna, Austria; *G.D. Burrows*, Department of Psychiatry, University of Melbourne, Australia; *B. Davies*, Department of Psychiatry, University of Melbourne, Australia; *J.M. Davis*, Illinois State Psychiatric Institute, Chicago, Ill. USA; *E. Elonen*, Department of Pharmacology, University of Helsinki, Finland; *W.E. Fann*, Department of Psychiatry, Baylor College of Medicine, Houston, Texas, USA; *R.O. Friedel*, Department of Psychiatry and Behavioral Sciences, University of Washington, Seattle, Wash. USA; *H.L. Goldberg*, West-Ros-Park Mental Health Center, Hyde Park, Mass. USA; *B.J. Goldstein*, Departments of Psychiatry and Pharmacology, University of Miami, Florida, USA; *L.H. Hollister*, Veterans Administration Hospital, Palo Alto, Calif. USA; *J.W. Jefferson*, Department of Psychiatry, University of Wisconsin-Madison, USA; *I. Keracan*, Department of Psychiatry, Sleep Disorders Center, Baylor College of Medicine, Houston, Texas, USA; *A. Kiev*, Cornell University Medical College, New York, NY, USA; *M. Kimura*, Psychotherapeutic Internal Department, Kyushu University, Fukuoka, Japan; *N.S. Kline*, Department of Mental Hygiene, Rockland Research Institute, Orangeburg, New York, USA; *A.J. Krakowski*, Plattsburgh, NY, USA; *M. Lader*, Institute of Psychiatry, De Crespigny Park, London, England; *M. Mattila*, Department of Pharmacology, University of Helsinki, Finland; *E. Radmayr*, Facharzt fur Neurologie und Psychiatrie, Dornbirn, West Germany; *K. Rickels*, Department of Psychiatry, University of Pennsylvania, Philadelphia, Pa. USA; *M. Toru*, Department of Neuropsychiatry, Tokyo Medical and Dental School, Japan; *J.K. Vohra*, Cardiac Department, Royal Melbourne Hospital, Australia.

Table of Contents

Summary

Synopsis: *Doxepin[1] is closely related in structure and general pharmacological properties to other tricyclic antidepressant drugs such as amitriptyline and imipramine. It combines antidepressant activity with a sedative effect and in this respect resembles amitriptyline, with which it shares a similar profile of clinical action.*

The mood elevating effect of doxepin appears to be similar to that of amitriptyline but is probably less marked than that of imipramine and in some studies has been slower to take effect than imipramine. At dosages which have achieved a similar overall response rate, doxepin tends to cause fewer or less troublesome side-effects than imipramine, amitriptyline or amitriptyline-perphenazine. The more marked sedative properties of doxepin make it more useful than imipramine in depressed patients with sleep disturbances and in depression associated with anxiety. The benzodiazepines remain the drugs of choice in anxiety states, but when anxiety is accompanied by significant depression, doxepin is more effective than chlordiazepoxide or diazepam.

Doxepin is usually well tolerated, and in particular by the elderly and those with cardiovascular disease. Side-effects are similar in nature to those of other tricyclic antidepressants, with dry mouth, drowsiness and constipation being the most common. Postural hypotension is uncommon. Although doxepin appears to cause fewer cardiovascular side-effects in usual therapeutic doses, it has an intrinsic cardiotoxicity on overdosage similar to other tricyclics.

Pharmacodynamic studies: In rodents, doxepin has been shown to antagonize the central depressant effects of reserpine and tetrabenazine, to suppress spontaneous motility and conditioned avoidance behaviour, and to potentiate and prolong the stimulant actions of amphetamine and levodopa, to an extent similar to that observed with amitriptyline. Doxepin also possesses tranquillizing properties similar to the benzodiazepines, but it lacks muscle relaxant properties. Its central and peripheral anticholinergic properties are less than those of amitriptyline, and the cardiovascular effects are similar to other tricyclics — lowered blood pressure, increased heart rate, reduced total peripheral resistance and, at higher doses, cardiac arrhythmias. Compared with other tricyclic antidepressants, doxepin is only a weak inhibitor of norepinephrine or serotonin uptake into peripheral organs or the brain, although it potentiates pressor responses to norepinephrine and blocks those to tyramine.

In man, doxepin produces EEG changes typical of the tricyclic antidepressants. Its cardiovascular effects are minimal, even in patients with myocardial disease, and hypotension has occurred in only a small proportion of patients during therapy. Doxepin, unlike other tricyclic antidepressants, appears to have little effect on intracardiac conduction, but like other tricyclic antidepressants, it disturbed cardiac rhythm on overdosage. Doxepin potentiates

1 'Sinequan', 'Sinquan' (Pfizer); 'Adapin' (Pennwalt); 'Aponal', 'Curatin', 'Quitaxon' (Boehringer Mannheim)

pressor responses to epinephrine, blocks those to tyramine, and at doses above 200mg daily reverses the antihypertensive effects of adrenergic neuron blocking agents like guanethidine and bethanidine. A major metabolite of doxepin, desmethyldoxepin, is pharmacologically active. Thus in the body, pharmacological effects are exerted by a mixture of doxepin and its active metabolite(s).

Pharmacokinetic studies: Results of experiments in rats and dogs using radio-labelled doxepin, show it to be well absorbed after oral administration, rapidly distributed to various tissues including liver, kidney, lung and brain, and rapidly metabolised by pathways similar to amitriptyline and imipramine. About 50 to 60% of an oral dose was excreted in the urine in 24 hours. In a preliminary study in elderly patients, therapeutic plasma levels of total drug (doxepin plus desmethyldoxepin) appeared to be about 110ng/ml, and were associated with a dose range of 50 to 300mg daily. Another study in depressed patients suggests that clinical response correlates with plasma levels of desmethyldoxepin of 20ng/ml or above, but not with plasma levels of doxepin alone.

Therapeutic trials: When confounding effects due to study population differences are eliminated and the similar overall response rate in uncontrolled and comparative trials is taken into account, together with the superior results of doxepin over a placebo, one must conclude that doxepin is an active antidepressant. Whether it is definitely as effective overall as amitriptyline and imipramine in depression must await clarification in studies involving a large number of patients. Trials involving relatively small numbers of patients in well-matched treatment groups have not been able to detect a statistically significant overall difference between doxepin and amitriptyline or imipramine. Nevertheless, trends for differences in certain types of depression have emerged. From both the comparative trials and the clinical experience in uncontrolled trials, doxepin seems to have mood elevating activity probably less marked than that of imipramine but similar to that of amitriptyline. Thus in the largest uncontrolled trial doxepin was most effective in agitated depressives and of lesser benefit in retarded depressives. In the largest comparative trial, doxepin tended to be more effective than imipramine in neurotic depression, while imipramine was more effective in endogenous depression. Doxepin also tends to be more effective than imipramine in depressed patients with sleep disturbances. Similar differences between doxepin and amitriptyline have been less evident, possibly because both have mood elevating properties as well as pronounced sedative activity. Doxepin cannot be regarded as superior to other tricyclic antidepressants in the treatment of severe, endogenous depressions.

It is possible that doxepin may have a more prominent sedative effect than amitriptyline because in general, doxepin has tended to produce a more favorable response than amitriptyline in patients with depression associated with anxiety or the mixed depression-anxiety syndrome. Doxepin has achieved a similar response as amitriptyline-perphenazine in these patients, but appears to be better tolerated. The antianxiety effect of doxepin occurs earlier than its antidepressant effect, and more rapidly than that of amitriptyline or amitriptyline-perphenazine. The onset of antidepressant effect of doxepin is similar to that of amitriptyline or amitriptyline-perphenazine, but in some studies was less rapid than that of imipramine. Preliminary findings suggest that the onset of antidepressant effect of doxepin may be more rapid with a single daily bedtime dosage regimen than with a divided daily dose schedule.

In preliminary studies, doxepin appears to have a lesser depressive effect on intracardiac conduction than imipramine or amitriptyline. It has been well tolerated by patients with myocardial disease, although patient numbers have not been very large, and by the elderly in whom postural hypotension and antichoiinergic side-effects have not proved a problem.

The effects of doxepin in anxiety states are not such that it can be considered in preference to the benzodiazepines, but when a predominant anxiety state is accompanied by depression, doxepin has proved superior to chlordiazepoxide and diazepam and to be associated with a much smaller incidence of ataxia.

Side-effects are generally mild and tend to disappear with continued treatment, or if necessary, reduction of dosage. The most common side-effects have been dry mouth, drowsiness, constipation and dizziness. Excessive daytime drowsiness or sedation can be overcome by giving the major portion or the total daily dose at bedtime. Other side-effects are typical of tricyclic antidepressants and have occurred much less frequently. Hypotension and tachycardia in particular have been uncommon with doxepin. The usual precautions for use of tricyclic antidepressants also apply to doxepin.

Doxepin has only a moderate effect on the norepinephrine pump. Consequently, only at doses of 200mg or more daily has it antagonised the antihypertensive effect of guanethidine or bethanidine. In cases where doxepin has antagonized the antihypertensive effect of guanethidine or bethanidine, and the blood pressure has returned to pretreatment hypertensive levels, *abrupt* withdrawal of doxepin has been followed by a rebound *increase* in diastolic pressure to dangerously high levels above the pretreatment value.

Dosage should be individualised. The usually effective dosage for most depressed patients has been 75 to 150mg daily for outpatients and 150 to 300mg daily for hospitalised patients. A few patients have required larger doses. Doses for the elderly should be smaller initially, with smaller progressive increases. Patients with anxiety have usually been treated with 75 to 150mg daily, but hospitalised patients and some other patients may require larger doses. A dosage regimen based on the major portion or total daily dose given at bedtime has been of benefit in depressed patients with sleep disturbances, in the elderly and when it has been necessary to avoid any excessive daytime drowsiness. Dosage increases of tricyclic antidepressants should always be gradual, particularly in bedtime-based schedules.

This review completely updates that previously published in the journal (Brogden et al., 1971). Since our original evaluation, many additional studies on the pharmacology and therapeutic use of doxepin have been published. These have been reviewed along with the previous data with particular emphasis on re-evaluation of the antidepressant properties and efficacy of doxepin.

1. Pharmacodynamic Studies

Doxepin is a derivative of dibenzoxepin, and is structurally related to other tricyclic antidepressant drugs such as amitriptyline and imipramine (fig. 1). It is a 15:85% mixture of the *cis*- and *trans*-isomers of N,N-dimethyldibenz (b,e) oxepin-$\Delta^{11(6H)}$,3-propylamine.

1.1 Animal Studies

The pharmacological profile of doxepin combines significant activity in animal models of depression with pronounced sedative and tranquillizing properties. It also possesses peripheral and central anticholinergic activity, together with antispasmodic and mild peripheral vasodilating effects. In virtually all these tests, the *cis* geometric isomer of doxepin is more active than doxepin itself, which in turn is more active than its *trans* isomer. Desmethyldoxepin, a major metabolite of doxepin, is pharmacologically active and has more marked sedative properties than doxepin. Wide variation in experimental design, species and test preparation used, dose and method of administration, often made interpretation of the data difficult. Doxepin produces dose-dependent decreases in blood pressure, increases in heart rate, and cardiac arrhythmias in most species; at corresponding dose levels greater than therapeutic doses in man.

1.1.1 Antidepressant Activity

Evaluation of psychotherapeutic drugs is made difficult by the lack of true animal equivalents of human disease. The antidepressant activity of the tricyclic compounds was originally demonstrated in animals by their mode of interaction with other centrally acting drugs, and later by certain peripheral and central biochemical effects.

In rats and mice, intraperitoneal doses of doxepin 5 to 40mg/kg produced a dose-dependent reversal of reserpine-induced catalepsy and ptosis, though openfield behaviour in reserpine-treated animals was unaffected (Hano et al., 1972). Doxepin was less potent than amitriptyline and imipramine in antagonizing reserpine-induced hypothermia in mice (Ribbentrop and Schaumann, 1965; Van Reizen and Delver, 1971), with a major metabolite of doxepin, desmethyldoxepin, being as active as doxepin itself (Ribbentrop and Schaumann, 1965) and the *cis* isomer of doxepin being more active than its *trans* isomer (Schaumann and Ribbentrop, 1966). In another study, both the *cis* and *trans* isomers were as active as doxepin itself in antagonizing reserpine-induced hypothermia in mice (Otsuki et al., 1972b). The central depressant actions of tetrabenazine were reversed by doxepin (cited in Brogden et al., 1971).

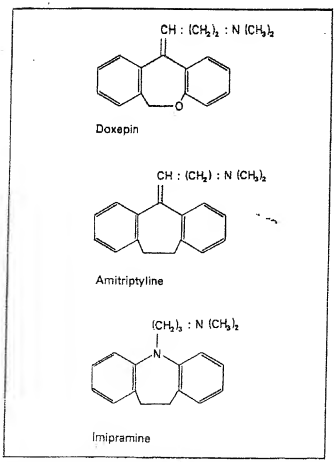


Fig. 1. Structural formulae of doxepin, amitriptyline and imipramine.

In animal behaviour tests of antidepressant activity, doxepin was about twice as potent as imipramine in potentiating the stimulant action of levodopa given with the monoamine oxidase inhibitor pargyline in mice (Hano et al., 1972). Effects on locomotor activity depended on the dose. At doses of 6.25 to 12.5mg/kg in mice, doxepin potentiated spontaneous locomotor activity, whereas higher doses (20 to 50mg/kg) inhibited hyperactivity (Hano et al., 1972; Zielinski et al., 1973). In this test, *cis*-doxepin has greater activity than doxepin or its *trans* isomer (Otsuki et al., 1972b).

According to the biogenic amine hypothesis of depression (Schildkraut, 1970), tricyclic antidepressants have been held to act by inhibiting the amine (e.g. norepinephrine) reuptake pump in the neuronal membrane, thus making more amine available to function as a neurotransmitter in the brain. Methods do not exist for measuring directly the uptake of biogenic amines in the brain of man. Thus, data obtained from the peripheral study of biogenic amine mechanisms, which when coupled with data from animal studies, are used as an indirect inference of central amine effects in man. Drugs which affect 5-hydroxytryptamine (serotonin) uptake by platelets or affect the amine pump in the peripheral adrenergic neuron, influence brain uptake mechanisms in a similar manner. The peripheral effect of tricyclic antidepressants on biogenic amines is also evaluated by their alteration of blood pressure responses to pressor agents and their inhibition of the action of adrenergic neuron blocking drugs such as guanethidine (Fann et al., 1971, 1974).

Doxepin was similar in potency to amitriptyline and imipramine but of lesser potency than

desipramine in blocking the uptake of norepinephrine into the rat heart (Koe and Constantine, 1972; Mundo et al., 1974), but unlike desipramine it did not block guanethidine-induced pressor blood pressure responses in the cat (Koe and Constantine, 1972). On the other hand, in the isolated rabbit heart, doxepin was much more potent than amitriptyline, desipramine or imipramine in inhibiting norepinephrine uptake (Barth et al., 1975). At concentrations of 10^{-6}M to 10^{-5}M, doxepin inhibited the *in vitro* uptake of norepinephrine into rat brain slices by about 30 to 40% in the hypothalamus, midbrain and pons/medulla oblongata areas, but by almost 60% in the striatum (Zielinski et al., 1973). Its effects in this respect seemed to be markedly weaker than those of imipramine reported in other studies (Glowinski and Axelrod, 1965).

Studies with rat (Buczko et al., 1974) and rabbit (Tuomisto, 1974) blood platelets have established that doxepin and desipramine, compared with amitriptyline, imipramine and most of their congeners, are weak inhibitors of 5-hydroxytryptamine (5-HT) uptake. This order of potency prevailed when 5-HT uptake into rat brain synaptosomes was studied (Tuomisto, 1974). Most of the activity of doxepin in this test appeared to reside in the *trans*-isomer, which comprises 85% of the commercially available drug, for the *cis*-isomer was virtually ineffective (Buczko et al., 1974).

These findings suggest that doxepin and desipramine would only be considered weak antidepressants on the basis of 5-HT uptake data. However, such properties may not be a prerequisite for antidepressant activity since iprindole and mianserin have little or no effect on biogenic amine uptake, yet are clinically active antidepressants (Coppen et al., 1976; Fann et al., 1974). Moreover, desipramine is a potent inhibitor of norepinephrine uptake in man (Oates et al., 1969). Furthermore, although doxepin may have only moderate effects on biogenic amine metabolism in most test preparations, it is likely that its metabolite desmethyldoxepin, being a secondary amine, would have important effects. In the body, one is dealing with a mixture of doxepin and its active metabolite(s) and no implications can necessarily be drawn regarding effect on biogenic metabolism from isolated organ or *in vitro* test preparation studies.

Doxepin does however, potentiate the synaptic inhibitory effect of biogenic amines to a similar (norepinephrine) or greater (dopamine) extent than imipramine. Tehrani et al. (1975) showed that doxepin and imipramine were indistinguishable in their dose-dependent potentiation of the inhibitory effects of norepinephrine on electrically-induced postganglionic potentials in the superior cervical ganglion of the cat, but doxepin was significantly more potent than imipramine in its potentiation of the less pronounced dopamine-induced suppression of ganglionic transmission. Tricyclic antidepressants appear to inhibit the enzyme adenylate cyclase which is thought to resemble the dopamine receptor; with doxepin and amitriptyline being more potent than imipramine or desipramine (Karobath, 1975).

Doxepin (3mg/kg) had only a limited effect on potentiating pressor responses to norepinephrine in conscious rabbits; being similar in activity to amitriptyline (2.5mg/kg), but less active than protriptyline (2.5mg/kg) or nortriptyline (2.5mg/kg) [Elonen et al., 1974]. Amitriptyline and doxepin produced similar dose-dependent potentiation of norepinephrine responses in the spontaneously beating rabbit heart (Elonen et al., 1974). In anaesthetized cats, doxepin 5mg/kg did potentiate pressor responses to norepinephrine, and in common with most other tricyclic antidepressants it reduced the pressor effect of epinephrine (Constantine et al., 1964; Otsuki et al., 1972a).

Another hypothesis of depressive illness associates the disorder with a change in the type B form of human monoamine oxidase. Doxepin, like other tricyclic antidepressant drugs, showed a greater affinity for the B- than for the A-form of rabbit lung mitochondrial monoamine oxidase. It was of similar potency as protriptyline, but was only about half as potent as amitriptyline in inhibiting the deamination of phenethylamine (substrate for B form) or 5-hydroxytryptamine (substrate for A form). Imipramine and desipramine were however, slightly less potent

than doxepin in inhibiting deamination of phenethylamine. Doxepin also inhibited human platelet MAO deamination of phenethylamine (to a greater extent than the B form of rabbit lung oxidase) at concentrations similar to those required in other studies of amitriptyline or imipramine (Roth, 1975). Doxepin also inhibited MAO activity in purified beef brain mitochondria, but in this test 5-hydroxytryptamine showed greater susceptibility than phenethylamine (Gabay et al., 1975).

1.1.2 Tranquillizing and Sedative Properties

Doxepin seems to produce sedative or stimulant effects in animals depending upon the dose of drug, though sedative effects predominate. At doses of 6.25 to 12.5mg/kg (IP), doxepin stimulated spontaneous locomotor activity in mice, but higher doses of 20 to 100mg/kg depressed the central nervous system, causing ataxia and reduced motor activity (Hano et al., 1972; Wohlfarth-Ribbentrop and Schaumann, 1969; Zielinski et al., 1973). Desmethyldoxepin was much more active than doxepin in inhibiting spontaneous locomotor activity in mice (Ribbentrop and Schaumann, 1965). Doses of up to 50mg/kg orally had similar effects in dogs, and were generally associated with parasympathetic stimulation and mydriasis (Brogden et al., 1971). The sedative effect of doxepin was about equal to that of chlordiazepoxide in inhibiting spontaneous motility and curiosity in mice (Wohlfarth-Ribbentrop and Schaumann, 1969), as well as rearing and emotional defecation in the open field test in rats (Hano et al., 1972). Hyperactivity induced by pheniprazine and the reserpine-like benzoquinolizine Ro 4-1284 was inhibited by doxepin (Zielinski et al., 1973).

Although doxepin inhibited amphetamine-induced stereotypy in rats, especially compulsive gnawing, it did not antagonize apomorphine-induced stereotypy (Hano et al., 1972) and did not produce catalepsy in rats (Hano et al., 1972; Wohlfarth-Ribbentrop and Schaumann, 1969); thus ruling out any possibility of neuroleptic activity. At high (50mg/kg) and lower (5 to 10mg/kg) doses in mice and at lower doses in rats (5 to 25mg/kg), doxepin inhibited amphetamine-induced hyperactivity, whereas the hyperactivity was enhanced with high doses (50mg/kg) in rats (Hano et al., 1972; Zielinski et al., 1973). In another study in rats (Otsuki et al., 1972b), doses of 20mg/kg of both doxepin and in particular its *cis* isomer enhanced amphetamine-induced hyperactivity, whereas the *trans* isomer tended to antagonize the hyperactivity.

Doxepin and imipramine were more potent than amitriptyline or desipramine, but less potent than chlorpromazine and haloperidol in inhibiting hyperactivity in rats induced by the 5-HT depleting agent *p*-chloroamphetamine (Lassen, 1974).

Doxepin suppressed conditioned avoidance responses in rats only in large doses (> 40mg/kg) which caused muscle relaxation, whereas chlordiazepoxide, thioridazine and chlorpromazine inhibited conditioned responses at doses which caused sedation (Wohlfarth-Ribbentrop and Schaumann, 1969). In mice, 10 to 30mg/kg doses of doxepin produced a progressively greater suppression of avoidance behaviour. The effect of 10mg/kg doxepin was similar to that of amitriptyline but more marked than that of desipramine (Kulkarni and Bocknick, 1973). Other investigators have also demonstrated dose-dependent suppression of conditioned avoidance behaviour in rats, with doxepin being similar in potency to amitriptyline (Tadokoro, 1972a,b). The *cis* isomer of doxepin appears to be slightly more potent than doxepin or its *trans* isomer in inhibiting conditioned avoidance behaviour (Otsuki et al., 1972b).

The reserpine-like compound Ro 4-1284 blocks avoidance behaviour in mice; an action which was antagonized by amitriptyline and doxepin and to a lesser extent desipramine when given in low doses, but which was more consistently potentiated by high doses of amitriptyline and doxepin. Only at toxic doses did desipramine potentiate the Ro 4-1284 effect (Kulkarni and Bocknick, 1973). This may mean that drugs such as amitriptyline and doxepin, which have both antidepressant and antianxiety effects (see section 3.1), depending on dose are capable of both antagonizing and potentiating the effects of reserpine-like compounds on conditioned avoidance responses.

In operant conditioning schedules in rats, doxepin produced a dose-dependent depression of food-reinforced responses, equipotent with amitriptyline and imipramine but more potent than butriptyline. Unlike diazepam, pentobarbital, chlorpromazine and haloperidol, the avoidance-reinforced response was only slightly depressed by doxepin and the other tricyclic antidepressants and then at the highest doses (Molinengo and Ricci-Gamalero, 1972).

Doxepin was similar in potency to amitriptyline or chlorpromazine in suppressing aggression in isolated mice, but although less potent than chlorpromazine was more active than amitriptyline in potentiating the sedative action of urethane (Ribbentrop and Schaumann, 1965), with desmethyldoxepin being more potent than doxepin in potentiating urethane-induced sedation but less potent in inhibiting aggression of isolated mice (Ribbentrop and Schaumann, 1965). The *cis* isomer of doxepin was more active than its *trans* isomer in potentiating urethane-induced sedation (Schaumann and Ribbentrop, 1966). Doxepin and amitriptyline were equipotent in prolonging hexobarbital-induced sleep in mice (cited in Brogden et al., 1971), with the *cis* isomer being more potent than doxepin or its *trans* isomer (Otsuki et al., 1972b). Spontaneous electrical activity in monkey brains was depressed by doxepin in a similar way to that seen with amitriptyline (cited in Brogden et al., 1971).

1.1.3 Anticholinergic Activity

Doxepin, like amitriptyline, possesses peripheral anticholinergic activity as evidenced by the production of mydriasis in mice, and central anticholinergic activity as shown by the protection of mice against the toxic effects of the cholinesterase inhibitor paraoxon (Ribbentrop and Schaumann, 1965); with desmethyldoxepin being less active than doxepin (Ribbentrop and Schaumann, 1965) and the *cis* isomer of doxepin being more active than the *trans* isomer (Schaumann and Ribbentrop, 1966). Doxepin was less potent than amitriptyline, but more potent than imipramine, in producing mydriasis in mice and in blocking methacholine-induced mortality in mice (cited in Brogden et al., 1971; Otsuki et al., 1972a) with the *cis* isomer being more potent than doxepin or its *trans* isomer (Otsuki et al., 1972b).

Like other tricyclic antidepressants, doxepin produced atropine-like central effects in conscious rabbits (Moore and White, 1975). It produced dose-dependent mydriasis and EEG synchronisation, at levels of 1 to 5mg/kg (iv), without producing overt signs of sleep. Similar levels of doxepin also inhibited in a dose-dependent manner the EEG activation produced by physostigmine or methamphetamine, but its influence on the behavioural effects of methamphetamine was, like that of atropine, enhancement. These results are in contrast to those with antipsychotic agents like chlorpromazine and haloperidol, which cause miosis, and block the EEG and behavioural arousal caused by methamphetamine without blocking the EEG activation caused by physostigmine.

Like atropine, doxepin also produced significant hypotension in conscious rabbits (Moore and White, 1975). It is unlikely that an anticholinergic component is involved in the cardiotoxic effects of doxepin, however, since in rodents its tachyarrhythmic effects were unaffected by large doses of atropine or physostigmine, but blocked by β-adrenoceptor antagonists (Elonen, 1975; see section 1.1.5).

In vitro studies of the anticholinergic activity of doxepin have used models of the central and peripheral muscarinic receptors, namely cholinergic receptor binding in rat brain homogenates and the guinea pig ileum (Synder and Yamamura, unpublished data; reported in Ayd, 1975a). Doxepin was less potent at both receptors by a factor of 4 than was amitriptyline, which had an affinity for central receptors of 10nM and for peripheral receptors of 27nM (about 1/20th of atropine in each case). Imipramine, which was equipotent at both receptors, was more potent than doxepin at peripheral receptors (74cf 100nM) but less so at central receptors (78cf 44nM).

1.1.4 Antispasmodic Activity

At concentrations of less than 1μg/ml, doxepin inhibited spasm induced by 5-hydroxytryptamine creatinine sulphate (5-HT) 1.5μg/ml, by histamine

2.5μg/ml, acetylcholine 0.2μg/ml and barium chloride 100μg/ml, in isolated guinea pig ileum. The antagonism of 5-HT and acetylcholine was less pronounced in isolated guinea pig trachea than on ileum. The anticholinergic action was relatively weak in both preparations compared with the antagonism of 5-HT or histamine, and this order of potency prevailed in intact guinea pigs with bronchospasm induced by the three transmitter substances. Doxepin also caused a 25 to 100% inhibition of epinephrine (adrenaline)-induced contractions of rabbit aortic strips at concentrations of 0.001 and 0.1μg/ml respectively, with inhibition of angiotensinamide-induced contractions only at considerably higher (100μg/ml) concentrations (Constantine et al., 1964). Doxepin is less potent than amitriptyline in inhibiting acetylcholine-induced spasm in isolated guinea pig ileum (Otsuki et al., 1972a), with the *cis* isomer being more potent than doxepin and its *trans* isomer (Otsuki et al., 1972b).

1.1.5 Cardiovascular Effects

In most animal species, intravenous doxepin generally lowers blood pressure, increases heart rate, and provokes cardiac arrhythmias. Intracardiac conduction blockade may be responsible for the arrhythmic effects, because norepinephrine potentiation (Elonen et al., 1974) and anticholinergic effects appear not to play an important part (Elonen, 1975).

In cumulative doses up to about 9 to 15mg/kg in mice, doxepin caused tachyarrhythmias, leading at higher doses (> 20mg/kg) to a progressive and finally lethal bradycardia (Elonen, 1975). In one study (Ribbentrop and Schaumann, 1965), doxepin and amitriptyline had an electrocardiographic effect indistinguishable from ajmaline; a drug with quinidine-like properties. The membrane effects of doxepin and amitriptyline were confirmed in another study; as evidenced by their ability to produce local anaesthesia on the rabbit cornea and stabilize human red blood cells against hypo-osmotic hemolysis (Elonen, 1974). Ventricular arrhythmias and a decrease in atrioventricular conduction were produced by sympathetic nerve stimulation in the isolated rabbit heart during perfusion with doxepin or desipramine, but not when propranolol was added to the perfusate or when the heart was exposed to iprindole, cocaine, atropine or control saline. Quinidine did not prevent the doxepin- or desipramine-induced arrhythmias (Barth and Muscholl, 1974; Barth et al., 1975). Elonen (1975) also found that β-adrenoceptor blocking drugs, but not atropine or physostigmine, produced dose-dependent inhibition of doxepin-induced tachyarrhythmias in mice. None of the drugs prevented or postponed death. Indeed, large doses of β-blockers enhanced (in a dose-dependent manner) bradycardia and accelerated death. The cardioselective β-blocker metoprolol, which lacks membrane stabilizing (local anaesthetic) and intrinsic sympathomimetic activity, was the most effective in preventing tachyarrhythmias, and with practolol (which also lacks membrane stabilizing but possesses intrinsic sympathomimetic activity) proved less active in enhancing bradycardia than tolamolol, propranolol and alprenolol, which do possess membrane stabilizing activity.

Slow intravenous injection of tricyclic antidepressants to conscious rabbits immediately lowered blood pressure and increased heart rate (Elonen et al., 1974; Moore and White, 1975). Amitriptyline and doxepin were more potent in this respect than protriptyline or nortriptyline, and also more frequently provoked severe arrhythmias; characterised by deepened and broadened S waves with ST changes in lead I and severely deformed QRS complexes (Elonen et al., 1974). The same effects and order of potency were noted when the antidepressants were given to conscious rabbits pretreated with protriptyline to block the membrane pump in adrenergic neurons during the period of the experiment (Elonen and Mattila, 1975). When the antidepressants were given during norepinephrine infusion their effects remained similar (Elonen et al., 1974), although in protriptyline pretreated animals the effect on blood pressure and heart rate was more pronounced (Elonen and Mattila, 1975).

The order of cardiotoxicity of these four tricyclic antidepressants in acute experiments in rabbits is

therefore the reverse of their order of potency in potentiating norepinephrine pressor responses due to inhibition of norepinephrine uptake (see section 1.1.1) but also the reverse of their order of cardiotoxicity in terms of time to death due to arrhythmias in guinea pigs (Burrows et al., 1976a) and in man, where doxepin appears to be less toxic than amitriptyline, imipramine or nortriptyline (see section 1.2.3). In another study (Barth et al., 1975), the rank order of potency of these antidepressants in inhibiting norepinephrine uptake in isolated rabbit hearts (doxepin > amitriptyline > desipramine > imipramine) appeared to be related to their ability to produce arrhythmias provoked by norepinephrine infusions, but inhibition of norepinephrine uptake does not by itself explain their cardiotoxicity; particularly since the incidence of arrhythmias with doxepin was closely comparable with that of amitriptyline and desipramine (5 times less potent as inhibitors of norepinephrine in the rabbit heart), although imipramine (12 times less potent as an uptake inhibitor than doxepin) did cause a much smaller incidence of arrhythmias. The cardiotoxicity of doxepin, amitriptyline, nortriptyline and protriptyline in anaesthetized rabbits did not correlate with either their heart concentration or heart/plasma concentration ratio; since the heart concentration of protriptyline, the least cardiotoxic, was highest, and since the heart/plasma ratios for amitriptyline and for protriptyline were much greater than doxepin, the most cardiotoxic (Elonen et al., 1975).

In anaesthetized dogs, doxepin produced a dose-related decrease in blood pressure and total peripheral resistance, a slight and transient increase in cardiac output, and a slight increase in heart rate. Intra-arterial doxepin was more potent than papaverine in increasing femoral arterial blood flow in dogs (Constantine et al., 1964). Otsuki et al. (1972a) also found that doxepin caused a fall in blood pressure accompanied by an increase in peripheral blood flow in dogs, with the potency of doxepin and its *cis* and *trans* isomers being similar (Otsuki et al., 1972b). Doxepin (and amitriptyline) were also more effective than adenosine in producing vasodilatation in the hind leg of the rabbit (Ribbentrop and Schaumann, 1965).

In the isolated cat heart, doxepin 50 to 200μg/ml produced a transient increase in coronary blood flow and a transient negative inotropic effect, which were maximal within 30 seconds of administration. The rate of contractions was decreased slightly by doxepin 200μg/ml (Constantine et al., 1964). In the isolated guinea pig atrium, doxepin and amitriptyline 20μg/ml produced a negative inotropic effect while 40μg/ml also exerted a slight negative chronotropic effect. A dose of 80μg/ml caused abrupt heart failure (Ribbentrop and Schaumann, 1965). In another study (Burrows et al., 1976b), at concentrations of 4 x 10^{-5}M, doxepin showed a significantly greater negative inotropic effect than either amitriptyline, imipramine, nortriptyline, protriptyline or desipramine on the isolated perfused guinea pig heart. The EKG showed non-specific ST-T wave abnormalities, prolongation of the PR interval and widening of the QRS complex. No difference was detected between the 6 tricyclics in the increase in the PR interval and QRS width. At higher concentrations of the 6 tricyclics, disturbances in excitability and conduction occurred, as evidenced by decreased heart rates, partial or complete atrioventricular block, and bizarre QRS complexes revealing right and left bundle branch blocks.

1.1.6 Anticonvulsant and Muscle Relaxant Activity

Doxepin prevented convulsions induced by pentylenetetrazole or maximal electroshock in mice, with ED_{50} values of 7.6 to 20mg/kg ip) respectively (Wohlfarth-Ribbentrop and Schaumann, 1969). This activity was also shown by diazepam (1.2 and 2.0mg/kg) and chlordiazepoxide (5.5 and 11.5mg/kg), but not by opipramol, thioridazine or chlorpromazine. In contrast to the benzodiazepines, however, doxepin did not affect strychnine-induced convulsions or mortality in mice (Wohlfarth-Ribbentrop and Schaumann, 1969). Doxepin was similar in potency to imipramine but less potent than amitriptyline in preventing nicotine-induced convulsions in mice, with diazepam being considerably

more potent than the tricyclic antidepressants (Aceto, 1975).

Muscle relaxant effects in mice (inclined plane) were seen with doxepin, as with the antipsychotic phenothiazines, only at dose levels several-fold higher than those required for sedative or tranquillising effects, whereas diazepam had muscle relaxant effects at doses slightly above those required for sedation (Wohlfarth-Ribbentrop and Schaumann, 1969).

1.1.7 Miscellaneous Effects

Doxepin and also amitriptyline inhibited the insulin release from the perfused rat pancreas, but to a lesser extent than cyproheptadine. Both early and late insulin secretion induced by a high glucose stimulus were suppressed (Joost et al., 1974). The mechanism of this inhibitory action is as yet unknown, but it may relate to the well known appetite stimulating effect of cyproheptadine and the ability of both doxepin (see section 4.3) and amitriptyline to cause a notable weight gain in some patients (Marble et al., 1976).

Tricyclic antidepressants can diminish pain reaction in laboratory animals. In a test involving induced rabbit dental pain, doxepin, amitriptyline, imipramine and trimipramine were more potent than nortriptyline, protriptyline and desipramine but less potent than morphine. Both doxepin and amitriptyline enhanced morphine analgesia. These effects were not related to the ability of the antidepressants to enhance norepinephrine pressor responses (Saarnivaara and Mattila, 1974). In man, tricyclic antidepressants have been used to relieve various types of pain, and in a well designed trial in depressed patients with chronic pain, doxepin had an analgesic effect unrelated to its ability to relieve depressive symptoms (see section 3.9.2).

Antidepressant drugs seem to inhibit prostaglandin biosynthesis. Thus, the monoamine oxidase inhibitors phenelzine and tranylcypromine, as well as the tricyclic antidepressants doxepin and desipramine were potent inhibitors of prostaglandin E_2 and $F_{2\alpha}$ biosynthesis in guinea pig lung. Phenelzine was even more potent than indomethacin (Lee, 1973). The significance of this finding to affective illness in man has yet to be determined, particularly since the antipsychotic drug chlorpromazine also inhibited prostaglandin biosynthesis.

1.1.8 Toxicology Studies

Acute Toxicity: The intravenous LD_{50} was 14.6 to 19.6mg/kg in mice, 12.7 to 18.8mg/kg in the rat and approximately 16mg/kg in the dog, while the oral LD_{50} was 148 to 178mg/kg, 346 to 460mg/kg and approximately 200mg/kg in mice, rats and dogs respectively (cited in Brogden et al., 1971; Noguchi et al., 1972a). In another study (Ribbentrop and Schaumann, 1965), the intravenous LD_{50} was 23 to 30mg/kg in mice (amitriptyline 18 to 22mg/kg), 14 to 19mg/kg in rats and 8 to 14mg/kg in rabbits (amitriptyline 6 to 11mg/kg), while the oral LD_{50} was 117 to 156mg/kg in mice (amitriptyline 100 to 216mg/kg) and 114 to 190mg/kg in rats (amitriptyline 286 to 359mg/kg). Noguchi et al. (1972a) also found doxepin to have a lower acute oral toxicity in rats and dogs than amitriptyline.

Administration of a toxic dose of doxepin usually results in death within 5 minutes if given intravenously and within 1 hour if given orally. Toxic signs in all species generally include central nervous system effects such as ataxia, general and respiratory depression, tremors, convulsions, prostration then death. Peripheral vasodilatation and/or constriction, piloerection and exophthalmia, have been noted occasionally, while in dogs, urination, defecation, vomiting and extensor rigidity have also been noted (cited in Brogden et al., 1971; Noguchi et al., 1972a). In urethane anaesthetized mice, doxepin was better tolerated than amitriptyline. The cause of death was severe cardiac arrhythmia. Pulmonary oedema was also noted (Ribbentrop and Schaumann, 1965).

Sub-Acute Toxicity: No macroscopic, microscopic, hematologic or biochemical changes were observed in dogs given 25 to 50mg/kg daily for 30 days. Mild sedation and vomiting occurred at a dose of 25mg/kg, and increased heart rate, miosis, sedation and twitching was observed at a dose of 50mg/kg (cited in Brogden et al., 1971).

A 5-week study in rats, three given either 200, 150, 100, 50 or 25mg/kg of doxepin daily, revealed normal haematologic and urinalysis values (cited in Brogden et al., 1971; Noguchi et al., 1972b). Most of the animals died at the highest dose levels, some of those at the dose of 100mg/kg daily and 1 at the dose of 50mg/kg daily. A decrease in body weight gain occurred in the higher dose groups, the effect being more pronounced in males than females. No adverse effects were detected on autopsy or following microscopic examination. In a similar study, amitriptyline appeared to be more toxic than doxepin, as evidenced by degenerative changes in the liver of the dead animals (Noguchi et al., 1972b).

Chronic Toxicity: Ptosis, sedation, tremors and vomiting occurred in dogs given 50mg/kg daily for 1 year. There were occasional episodes of vomiting at 25mg/kg but those given 5mg/kg were practically asymptomatic. There were no abnormal laboratory test values.

Fatty metamorphosis of the liver in the males, and inhibition of weight gain in the females, was observed in rats fed 100mg/kg of doxepin daily over a period of 18 months. Slight hepatic fatty metamorphosis was observed in rats given doxepin 50mg/kg daily for 1 year (cited in Brogden et al., 1971). No adverse effects were detected in rats given 5, 10 and 20mg/kg daily orally for 180 days, while higher doses of 80mg/kg daily in males and females, and 40mg/kg daily in males, caused a decrease in weight gain but no deaths. Aspiration lipoid pneumonia was seen on microscopic examination in sacrificed animals in the 40 and 80mg/kg daily groups (Noguchi et al., 1972c).

Reproduction and Dysmorphology Studies: There were no changes observed in litter size, number of live births or lactation in animals (species not stated) given doxepin at dosages of up to 25mg/kg daily for 8 or 9 months. A decreased conception rate resulted when male rats were given doxepin 25mg/kg daily for prolonged periods (time not stated). This effect has also been observed in animals given other psychotherapeutic agents. Macroscopic and microscopic examination of the offspring revealed no evidence of drug-related dysmorphogenic effects (unpublished data cited in Brogden et al., 1971). However, at oral dosages of 90 and 270mg/kg (a dose level greatly exceeding the maximum safety level) from day 9 to day 14 of gestation in pregnant rats, either death, miscarriage or reduction in body weight occurred in the dams and the mortality of fetuses at term was high, with a reduced body weight in live fetuses in the 270mg/kg group. The birth rate and survival rate at 3 weeks after birth was also decreased in the 270mg/kg group. All these effects were not observed in pregnant rats given 10 or 30mg/kg. No dysmorphogenic effects were noted, as determined by the absence of external, visceral or skeletal malformations (Owaki et al., 1971).

Tolerance and Dependence Studies: In doses up to 50mg/kg, doxepin, as with other tricyclic antidepressants, does not appear to have tolerance and physical dependence producing liability. Ten days treatment did not reveal tolerance to the inhibitory effect of doxepin on spontaneous locomotor activity in mice. Abnormal behaviour ascribable to physical dependence was not observed in mice and rats during or after abrupt withdrawal of forced drinking. Doxepin did not suppress abstinence signs elicited in barbital-dependent mice (Kaneto et al., 1972).

1.2 Human Studies

1.2.1 Effects on Electroencephalogram

In single-dose studies, doxepin has demonstrated EEG characteristics of both tricyclic antidepressants and anxiolytic drugs of the diazepam type (Simeon et al., 1969, 1970). However, during all-night polygraphic recording in depressed patients, who have usually had associated sleep disturbances, EEG changes have been similar in some respects to those produced by tricyclic antidepressants such as amitriptyline and imipramine, and different from hypnotics in some respects (Castogiovanni et al., 1971; Karacan et al., 1975, 1977; Karacan and Williams, 1976; Muratorio et al., 1967).

In an open clinical study in patients with anxiety, doxepin 100 to 300mg daily produced increases in theta activity and low voltage desynchronised activity without increasing fast activity, and was associated with the development of delta activity (Simeon et al., 1969). Single-dose studies in healthy volunteers showed that doxepin (0.27 to 0.36mg/kg, IM) produced increases in delta, theta and 24-35Hz activities, and decreases in amplitude and amplitude variability, and alpha bands (Simeon et al., 1969). Following intravenous administration over 2 minutes of 0.2mg/kg doxepin, identical changes were observed but were more rapid in onset (5 to 9 minutes) with a peak at 12 to 30 minutes. These changes were more similar to those produced by imipramine (0.45mg/kg) than by diazepam (0.15mg/kg), and markedly different from placebo (Simeon et al., 1970).

1.2.2 Effects on Biogenic Amine Metabolism

Animal studies have shown that doxepin is only a moderate inhibitor of norepinephrine uptake and a weak inhibitor of 5-hydroxytryptamine (5-HT) uptake by rat brain synaptosomes, as compared with other tricyclic drugs such as imipramine or amitriptyline, but that a marked effect on biogenic amine uptake may not necessarily be associated with antidepressant activity in man (see section 1.1.1). An *in vitro* study of 5-HT uptake in human blood platelets (Lingjaerde, 1976) showed that doxepin (K_i2 x 10^{-7}M) was about 30 times less potent than imipramine in blocking uptake, but about equipotent with nortriptyline and desipramine noted in animal studies. Doxepin in concentrations of up to about 10^{-4}M did not increase 5-HT efflux from platelets and the uptake inhibition below this rather high concentration is therefore reflecting a true reduction in influx.

Blockade of the norepinephrine uptake mechanism prevents the uptake of indirectly acting sympathomimetic amines and of adrenergic neuron blocking agents such as guanethidine. In man, the blocking effects of doxepin and other tricyclic antidepressants on uptake mechanisms can be assessed by its influence on the pressor actions of tyramine and norepinephrine and the antihypertensive actions of guanethidine and bethanidine (Fann et al., 1971). Doxepin appears to be less potent in these respects than some other tricyclic antidepressants such as desipramine, but nonetheless causes dose-dependent effects which can be clinically important (see section 6.2).

Following a dietary and placebo stabilisation period in 6 depressed patients, Fann et al. (1971) found that doses of 200 to 300mg daily of doxepin were required before the appearance of significant effects on biogenic amine metabolism or, in separate investigations, of effective antidepressant activity. Desipramine, on the other hand, shows marked effects on pressor responses to tyramine or norepinephrine at doses of only 75mg daily. A dose of 200 to 300mg doxepin was required to produce inhibition of the tyramine response similar to that seen with 100mg daily of desipramine. Potentiation of the pressor responses to norepinephrine were even less noticeable with doxepin than with desipramine. Average tyramine and norepinephrine sensitivities in 5 patients were 25% and 480% of control values respectively for desipramine 75 to 100mg daily, and 41% and 140% for doxepin 300mg daily. Tyramine and norepinephrine sensitivity returned to control levels within 4 days after withdrawal of doxepin therapy.

Doxepin also reduced platelet 5-HT content in depressed patients, an effect which is probably mediated through uptake inhibition. After 100mg daily for 7 days, the levels dropped to approximately one-half of control values, but there was no clear dose-response relationship with higher dosages (200 to 300mg). Platelet 5-HT levels also fell consistently after desipramine treatment. Doxepin did not alter urinary content of the principal 5-HT metabolite, 5-hydroxyindole-3-acetic acid (Fann et al., 1971).

1.2.3 Cardiovascular Effects

The overall incidence of hypotension associated with doxepin therapy has been given as 2.62% in 495 patients, in whom baseline and serial blood pres-

sure readings were made during continuous doxepin treatment (Pitts, 1969). This compares with an incidence of 8.56% for amitriptyline in parallel studies in similar patients. There has been no evidence for any increased risk of hypotensive effects of doxepin in elderly patients (Ayd 1975b) and Pitts (1969) has reported an incidence in this group of 3.61%.

In a group of healthy geriatric patients with memory deficits and behavioural problems, doxepin 25 to 150mg daily (mean 81.25mg) given at bedtime did not cause any adverse changes in EKG parameters. During the 12 week placebo-controlled trial, 1 patient with atrial fibrillation tolerated doxepin well while 3 patients with premature ventricular beats actually improved during doxepin treatment (Goldberg et al., 1975a). Ayd (1975b) found only transient tachycardia in some elderly patients receiving long-term therapy with doxepin, usually when dose-levels reached 200mg daily. Controlled trials in depressed or anxious patients with cardiovascular disorders have shown doxepin to be well tolerated (see section 3.5).

Measurements of cardiac performance in 32 ambulant depressed patients after 2 weeks of treatment with doxepin, amitriptyline or nortriptyline at doses of 50mg 3 times daily, showed increased PR-interval in all 32 patients with an increased heart rate in 26 patients, whatever the treatment (Burrows et al., 1976a; Davies et al., 1975; Vohra et al., 1975a,b). Right bundle branch block occurred in 3 patients, all on nortriptyline, and significant tachycardia in 1 patient on nortriptyline and one on amitriptyline. There were no changes in the corrected QT interval with any drug treatment. Patients receiving nortriptyline showed a significantly greater increase in PR-interval than those receiving doxepin. Doxepin may therefore have less effect on atrioventricular conduction.

A second study (Burrows et al., 1976a; Davies et al., 1975; Vohra et al., 1975b) evaluated intracardiac conduction in 12 depressed patients taking therapeutic doses of nortriptyline (150mg daily) using His bundle electrocardiography, an invasive sensitive EKG recording technique. Five of 12 patients who had plasma levels of nortriptyline over 200ng/ml showed prolongation of the HV interval (10 msec or more). One patient with marked prolongation of HV interval (80 msec) after nortriptyline was then changed over to doxepin in the same dosage, and the HV interval returned to normal.

In a cross-over comparison of 150mg/day dosage, 6 of 17 depressed patients on nortriptyline showed more than 25% prolongation of the QRS complex, whereas only 1 of the 17 patients while on doxepin experienced significant prolongation of the QRS complex, as measured by rapid recording surface electrocardiograms (Burrows et al., 1976b). The group of patients on doxepin had a mean plasma doxepin level of 52 ± 6ng/ml while those on nortriptyline had a mean plasma level of 196 ± 29ng/ml — levels of the order of those generally found during therapeutic use of these tricyclics (nortriptyline 174ng/ml in another study) with the same dosage and assay methods (see also section 2.2.2).

These investigators also studied intracardiac conduction in patients admitted to hospital after tricyclic antidepressant overdosage (Burrows et al., 1976a; Davies et al., 1975; Vohra et al., 1975c). Six patients who took more than 500mg doxepin (mean 1.3g per case) showed normal intracardiac conduction (normal HV interval). In contrast, 7 of 8 patients taking similar large overdoses of amitriptyline, nortriptyline or imipramine (mean 1.4g per patient) showed an abnormal HV-interval and a wide QRS, indicating prolonged intracardiac conduction (fig. 2).

On the basis of these series of studies, it would appear that doxepin may not depress the intracardiac conduction to the same extent as nortriptyline, amitriptyline or imipramine. However, these findings must not be interpreted to mean that doxepin is safe on overdosage, since lethal arrhythmias can still occur (see section 5).

Experiments with 25mg doses of intravenous doxepin (Schrieber, 1970), showed that it did not influence the tendency of patients to frequent extrasystoles, and prevailing disturbances in intraventricular conduction such as left bundle branch

block were not altered. There were no changes in cardiac rhythm or intracardiac conduction in well or poorly controlled digitalized patients with auricular fibrillation, although 1 well controlled patient experienced supraventricular extrasystoles.

1.2.4 Respiratory Effects

In a double-blind crossover trial (Steen and Thomas, 1973), each of 6 healthy volunteers received a single intramuscular injection of doxepin (0.3mg/kg), meperidine (0.5mg/kg), hydroxyzine (1.0mg/kg), diazepam (0.15mg/kg), or a combination of doxepin (0.2mg/kg) and meperidine (0.5mg/kg). The effects of doxepin alone on carbon dioxide stimulus curves were not significantly different from those of diazepam or hydroxyzine, and the classic respiratory depressant effects of meperidine were significantly reduced when given in combination with doxepin. However, respiratory depression can be severe in cases of massive doxepin overdosage (Williams, 1972; see section 5). At therapeutic doses, in 1 study, doxepin appeared to have no adverse effect on lung function in treated patients with bronchial asthma (Wiener, 1971), although in the course of a therapeutic trial, doxepin exacerbated bronchospasm in 3 treated chronic asthmatics (Gomide, 1969). Thus, doxepin, as with other drugs with sedative properties, should be used with caution in patients with chronic obstructive lung disease.

1.2.5 Effects on Psychomotor Skills

Doxepin may enhance the sedative effects of many central nervous system depressants (Ayd, 1973), but given alone it does not appear to significantly interfere with psychomotor skills. In combination with alcohol, however, it may impair driving skills.

In a double-blind crossover trial (Seppala et al., 1975), 20 healthy subjects took amitriptyline, doxepin

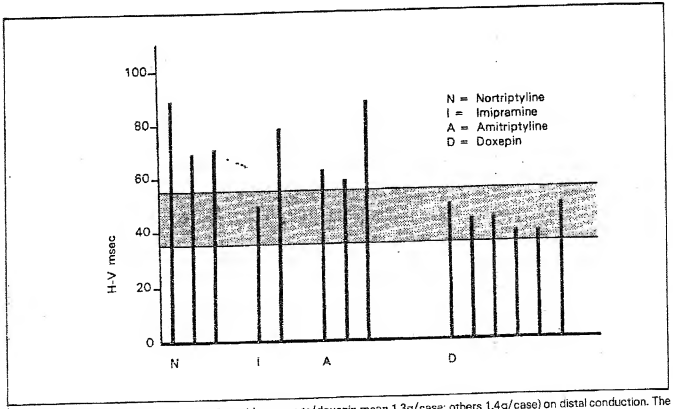


Fig. 2. Effect of overdosage of tricyclic antidepressants (doxepin mean 1.3g/case; others 1.4g/case) on distal conduction. The shaded area depicts normal H-V conduction time (after Burrows et al., 1976).

or placebo for 2 weeks each, and a similar group took nortriptyline, chlorimipramine or placebo. The antidepressants were given 3 times daily in doses of 30 to 60mg daily for amitriptyline, doxepin and nortriptyline, and 30 to 75mg daily of chlorimipramine. Patient compliance was checked regularly with the tyramine pressor test, and psychomotor skills (choice reaction, co-ordination, and attention) were measured before and after the administration of the drugs in combination with an alcoholic (0.5g/kg) or placebo drink on day 7 and 14 of each treatment period. The amount of tyramine needed to elevate the systolic blood pressure was significantly higher after 14 days of treatment with any of the 4 antidepressant drugs than after placebo, but there were no differences in psychomotor skills between subjects with high tissue levels of an antidepressant (as assessed by the tyramine test) and those with low levels. Blood alcohol concentrations (0.38ng/ml to 0.47ng/ml) over 90 minutes were not significantly modified during treatment with doxepin or amitriptyline. No antidepressant drug alone impaired psychomotor skills, but both amitriptyline and doxepin in combination with alcohol, increased both skills and the inaccuracy of reactions. Co-ordination was impaired by both of these combinations on the seventh day, but not by alcohol taken during administration of nortriptyline or chlorimipramine.

In another study, doxepin was shown not to enhance the effects of alcohol (Milner and Landauer, 1973). In a placebo-controlled study, 12 healthy volunteers received oral doses of 12.5 or 25mg/m^2 body surface area, given 12 hours apart. The subjects were tested, when sober and when 'intoxicated' by alcohol (blood levels of 73.6mg/100ml), in a number of psychomotor and psychological tests including two driving simulators. The only significant drug effect was an improvement in performance on one driving simulator by subjects receiving the higher dose of doxepin. Previous studies using the same techniques of assessment had revealed significant deleterious effects on performance by subjects consuming amitriptyline and alcohol.

2. *Pharmacokinetic Studies*

Pharmacokinetic studies have been conducted in rats and dogs, and to a much lesser extent in man. In animals, doxepin appears to be rapidly and completely absorbed following oral administration. The concentration of unchanged doxepin in blood is low, indicating rapid metabolism and distribution of the drug and its metabolites into tissue compartments. The major routes of metabolism appear to be similar to those of amitriptyline and imipramine, that is demethylation, N-oxidation, hydroxylation and glucuronide formation.

No data are available on the absorption, protein binding, apparent volume of distribution, plasma half life or possible hepatic first pass metabolism of doxepin or desmethyldoxepin in man.

2.1 Animal Studies

2.1.1 Absorption and Distribution

Following administration of single oral doses to rats and dogs, doxepin is well absorbed and plasma levels reach a maximum within 30 minutes to 1 hour, thereafter declining rapidly (Hobbs, 1969; Kimura et al., 1972). Plasma levels of unchanged drug are low. Initially, drug levels are high in the liver, kidney, spleen and lung (Hobbs, 1969; Kimura et al., 1972), but initial brain levels do not appear to be as high as those reported following similar doses of amitriptyline or imipramine (Hobbs, 1969). In rabbits, concentrations in the heart are 40 to 200 times greater than those measured in the plasma at the same time (Elonen et al., 1975). Appreciable amounts of the active metabolite desmethyldoxepin (Ribbentrop and Schaumann, 1965) are also found in tissues, and other metabolites in liver and urine, but only this demethylated metabolite and doxepin itself are found in brain (Hobbs, 1969; Kimura et al., 1972).

Doxepin appears to have an affinity for melanin of the eye where it is still detectable for up to 70 days after a single oral dose, but *in vitro* studies with beef eye ball show it to be less strongly bound than either amitriptyline or chlorpromazine (Hobbs, 1969).

Plasma and tissue concentrations of doxepin tend to increase with repeated or continued administration of the drug to rats. Tissue levels rapidly decline after administration is discontinued. Increases in tissue concentration are most marked, compared with single-dose administration, in liver, kidney, fat, muscle and eyeball, but there is no difference between light and dark skin (Kimura et al., 1972). In 3 dogs dosed over 5 days, plasma levels of doxepin and desmethyldoxepin usually reached a plateau by day 2 or 4 (Hobbs, 1969). Plasma levels of doxepin and its metabolites were still detectable 3 days after the last dose; in the dogs given 100mg daily for 5 days (Hobbs, 1969) or rats given 50mg/kg/day for 5 days (Kimura et al., 1972).

2.1.2 Metabolism and Excretion

The administered drug is excreted mainly in the urine. In the rat, 60% of the radioactivity administered appears in the 24-hour urine following single oral dosage, with about 25% in the faeces (Hobbs, 1969). Most of the dose in rats appears to be eliminated in the urine within 8 hours; very little is excreted in bile (Kimura et al., 1972). Excretion of unchanged doxepin is low, less than 5% in rats (Kimura et al., 1972). Identified metabolites in urine, faeces and bile in rats include desmethyldoxepin, doxepin-N-oxide, and a hydroxydoxepin and its glucuronide (Hobbs, 1969; Kimura et al., 1972). In dogs, the same metabolites have been recovered in urine as well as desmethyl hydroxydoxepin, but appreciable quantities of unchanged drug are also excreted (Hobbs, 1969).

2.2 Human Studies

2.2.1 Excretion

Urinary excretion studies in 7 healthy male volunteers, who received doxepin 25mg on day 1 and 50mg on day 3, showed that the excretion of doxepin and its desmethyl metabolite were less than 0.5% of the administered dose. Excretion was greatest after a 50mg dose, with most occurring during the periods 4 to 6 and 6 to 12 hours after oral administration. Metabolites corresponding to the desmethyl derivative, doxepin-N-oxide, and the hydroxylated derivative plus its glucuronide, were identified in human urine (Kimura et al., 1972).

2.2.2 Plasma Levels and Therapeutic Response

Therapeutic response appears to correlate with plasma levels of the active metabolite desmethyldoxepin or of doxepin plus desmethyldoxepin, but not with doxepin itself.

Kline et al. (1976) in a study of 10 adult outpatients with mild to moderate depression, observed a clinical response in all patients with plasma desmethyldoxepin levels of 20ng/ml or above, but a clinical response in only 1 of 7 patients with plasma levels below 20ng/ml. No such correlation existed between clinical response and plasma levels of doxepin itself. Nor did any correlation emerge between plasma levels and response in a group of 7 patients studied with anxiety.

In a study in 15 elderly depressed patients given doxepin in a single bedtime dose of 50 to 300mg*, plasma levels of total drug doxepin plus (desmethyldoxepin) averaged 60ng/ml (24 to 118) in 7 patients who experienced little or no therapeutic benefit (Friedel and Raskind, 1975). In contrast, the mean level was 111ng/ml (53 to 138) in 8 patients with marked to moderate improvement in depressive symptoms. The mean daily dose of doxepin in the two groups was 104mg (50 to 250) in the non-responders and 164mg (50 to 300) in the responders. However, there was variation in the plasma levels required for a therapeutic response in individual patients. In patients receiving 150mg daily, plasma levels of total drug (doxepin plus desmethyldoxepin) ranged from 24 to 131ng/ml, with no or marked improvement at either end of the range. One patient required 400mg daily* to achieve a therapeutic blood level of 281ng/ml, when marked improvement occurred, having experienced no improvement at 250mg or 100mg daily

* In the USA, the maximum recommended daily dose of doxepin is 300mg and in once-daily schedules the maximum recommended daily dose is 150mg.

(plasma levels of 107ng/ml and 33ng/ml respectively).

Subsequent studies have suggested that the active *cis* geometric isomers of doxepin and desmethyldoxepin appear to be converted in the body to the less active (in animals; see section 2) *trans* isomers. The extent of this conversion process varies from patient to patient and may result in levels of the *cis* isomers of doxepin and desmethyldoxepin approaching 30 to 40% of the total doxepin and desmethyldoxepin in the plasma (Friedel, pers. comm. 1976).

3. Therapeutic Trials

As with any psychotherapeutic drug, trials to detect antidepressant activity require careful design to eliminate subjective bias and control variables which can influence drug response. The most reliable results have generally come from double-blind trials of short duration in which large groups of patients have received the investigational drug, a standard agent and/or placebo in strictly regulated fashion (e.g. Smith et al., 1969).

There are numerous short-term double-blind comparative studies of doxepin in which the results have been assessed by the use of objective psychiatric symptom rating scales, particularly the Hamilton Rating Scales for various symptoms of depression and anxiety. Patient self-rating scales have also been used, and efficacy and side-effects have usually been globally rated (i.e. overall clinical effect) in most studies. Dosage has generally been flexible rather than fixed, in an attempt to optimise response. In common with virtually all present-day comparative drug trials, many studies with doxepin have however, included only small groups of patients, which makes it unlikely that any minor difference would be apparent between two active drugs expected to produce a similar response. Most comparative double-blind trials of doxepin and other drugs have not included a placebo control, thereby failing to demonstrate that the comparison drug was itself superior to placebo under the conditions of the trial; but those which did, have all shown a significant superiority of doxepin over placebo. Also, the use of a placebo run-in period prior to treatment with doxepin or other drugs has lessened this objection in some trials, by eliminating placebo responders from the trial population.

The selection of patients can also play an important role, and different trials have included patients with varying degrees of severity of illness and with varying elements of depression and anxiety in the overall symptomatology. Particular attention has therefore been given to analyse the composition of the patient groups of the various trials in an attempt to minimise confounding effects of population differences. The studies have therefore been classified and evaluated according to predominant symptomatology of the population studied, together with scrutiny for close matching of the treatment groups in the comparative trials.

3.1 Uncontrolled Trials in Depression

Numerous uncontrolled studies have shown doxepin to be an active antidepressant. These findings have been confirmed by its significant superiority over a placebo (Burrows et al., 1972; Guzman-Vilar, 1969; Kiev, 1974; Poeldinger and Peter, 1970) and by comparisons with other tricyclic antidepressants (section 3.2; table I).

In most uncontrolled trials, doxepin (depending on the population and criteria for improvement) achieved a marked response in from about 30 to 60% of patients, with moderate improvement in most others (Ayd, 1969; Belsasso et al., 1969; Bukowczyk et al., 1971; Krakowski, 1968; Mivelaz, 1969; Pitts, 1969; Poeldinger et al., 1966). A favourable response was noted in patients who had failed or not responded adequately to other treatment (Ayd, 1969; Bukowczyk et al., 1971; Diehl, 1971; Krakowski, 1968; Pitts, 1969) and in those with severe depression (Ayd et al., 1969; Diehl, 1971; Krakowski, 1968).

Some studies provided results according to nosologic classification. Patients with endogenous depression tend to respond as well or better than

Table I. Summary of results of double-blind comparative trials in depression

Author	Nosologic diagnosis	Population	Groups well matched[1]	Daily dosage doxepin (D)	Daily dosage other drug	Duration	Efficacy[2] (see also text)	Onset of response	Side-effects (see also text)	Response rate (%)[3]			
										doxepin		other	
										+ +	+	+ +	+
Comparison with amitriptyline (A)													
Bauer and Nowak (1969)	Endogenous (24) Other (6)	Outpts (30)	...	75-300mg	75-300mgA	4w	D = A	—	D = A	...	...	...	...
Bianchi et al. (1971)	Endogenous (29) Neurotic (21)	Outpts (15) Inpts (35)	?Yes	100-300mg (200mg)	100-300mgA (161mg)	35d	D = A	D < A	D < A	59	27	64	23
Blaine (1975)	Neurotic (25) Psychotic (12) Depression-anxiety (18) Other (3)	Outpts (58)	No (A)	25-250mg	25-250mgA	29d	D = A	—	D = A	71	25	77	13
Gomez-Martinez (1968)	Endogenous (17) Other (7)	Outpts (24)	—	100-200mg	100-200mgA	8w	D = A	—	D < A	45	18	58	8
Grof et al. (1974)	...	Inpts and Outpts (22)	No (D)	150-350mg	100-200mgA	4w	D = A	...	D < A	...	...	...	...
Hackett et al. (1967) Hackett and Kline (1969)	Neurotic (11) Other (3)	Outpts (14)	No (D)	150-200mg	25-150mgA	8w	D > A	...	D < A	...	...	...	...
Jones et al. (1972)	...	GP (63)	Yes	25-150mg	25-150mgA	8w	D = A	D = A	D < A	77	14	68	21
Solis et al. (1970)	Neurotic (18) Psychotic (10) Other (6)	Inpts (10) Outpts (24)	...	75-150mg	75-150mgA	8w	D = A	D > A	D = A	29	38	23	46
Toru et al. (1972)	Periodic (24) Cyclothymic (10) Neurotic (8) Other (13)	Outpts (53) Inpts (2)	Yes	75-300mg	75-300mgA	3w	D = A	D < A	D < A	13	26	4	42

Comparison with imipramine (I)													
Castrogiovanni et al. (1971)	Psychotic (44)	Inpts (44)	Yes	75-300mg (222mg)	75-300mg(I) (202mg)	24d	D = I	D < I	D < I	...	...	...	...
Goldberg et al. (1975b, 1976)	Neurotic (83) Other (14)	Outpts (97)	Yes	50-200mg	50-200mg(I)	2-4w	D = I	—	D = I	41	29	50	31
Hasan and Akhtar (1971)	...	Outpts (49)	...	75mg	75mg(I)	5w	D = I	D < I	D < I	38	38	24	59
Kimura et al. (1975)	Endogenous depression (50) Neurotic depression (60) Involutional depression (51) Mixed (23) Others (7)	Inpts (110) Outpts (81)	Yes	30-150mg	30-150mg(I)	6w	D = I	—	D < I	36	22	41	28

1 Population distribution favoured efficacy for drug indicated in parentheses, usually because of less patients with greater duration or severity of illness, and sometimes because of unequal distribution of patient types or previous treatment, etc. An elipsis (...) signifies insufficient information or not clear whether groups reasonably well matched. A dash (—) signifies no appropriate data provided. See also text.

2 Efficacy overall on basis of clinical (global) and psychiatric symptom rating scales. In many cases trends towards differences emerged between the study drugs. See text for explanation.

3 Response rate in terms of global clinical evaluation only. + + = remission or marked improvement; + = moderate improvement. (—) = no clinical assessment of results given; (...) = results not expressed as percentage. A figure only in + column signifies marked plus moderate improvement. See also text.

those with reactive or involutional depression (Bergener and Behrends, 1966; Garcia-Torres, 1968; Gillmer, 1970; Mivelaz, 1969). While some studies found patients with involutional depression to respond the least (Bergener and Behrends, 1966; Krakowski, 1968; Mivelaz, 1969) others have found the opposite (Pitts, 1969; Popovic et al., 1970). In the largest series (130 hospitalised patients), very little difference in marked response was apparent in these three nosologic categories (Poeldinger et al., 1966), although depressed schizophrenics responded poorly (Pitts, 1969; Poeldinger et al., 1966). Patients classified as having neurotic depression tend to respond better than those with psychotic depression (Pitts, 1969; Popovic et al., 1970). Those with manic-depressive psychosis (depressive phase) have responded well (Ayd, 1969, 1971, 1975b; Gillmer, 1970; Pitts, 1969). Patients with illness of more recent onset or of shorter duration tend to respond better (e.g. Krakowski, 1968; Poeldinger et al., 1966; fig. 3) and in two studies, women tended to respond more favourably than men (Ayd, 1969; Poeldinger et al., 1966).

Doxepin has a significant effect on symptoms of insomnia and anxiety with a significant but slightly lesser effect on agitation, depressed mood, psychomotor retardation, guilt, and suicidal ideation (Koknel and Eper, 1971; Moser, 1969; Pitts, 1969). Most investigators rated doxepin as similar to amitriptyline in its profile of antidepressant activity (e.g. Poeldinger et al., 1966; Poeldinger, 1966a,b; Elwan et al., 1976; van Praag, 1969). Both drugs have marked sedative properties in addition to mood elevating properties. Poeldinger et al. (1966) and Moser (1969) found doxepin to produce a more favourable response in the agitated-anxious depressive than in the inhibited-apathetic depressive. Elwan et al. (1976) considered amitriptyline (75 to 150mg daily) to have superior mood elevating properties, but dosages of doxepin used (75 to 100mg daily) in this uncontrolled trial were less than optimum. In controlled comparative trials in depression the dosage of doxepin found equivalent to amitriptyline has generally been the same or usually more (table I). Thus, the general con-

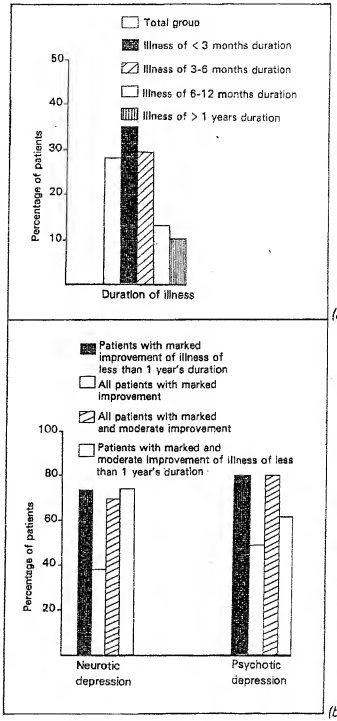


Fig. 3. (a) Response of 130 hospitalised depressed patients (% with marked improvement or remission) according to the duration of their illness (data from Poeldinger et al., 1966).

(b) Response of neurotic (40) psychotic (10) depressed patients according to the duration of their illness (data from Krakowski, 1968).

sensus from uncontrolled trials is that doxepin is similar to amitriptyline as an antidepressant.

In most studies, a minimum dosage of 75mg daily was needed to achieve improvement; with the most effective daily dosage ranging from 100/150 to 200/300mg daily (Ayd, 1969; Belsasso et al., 1969; Koknel and Eper, 1971; Poeldinger et al., 1966). A few patients with marked depression were benefited by larger doses (300 to 500mg* daily) without a significant increase in side-effects (Ayd, 1969; Koknel and Eper, 1971; Majczak et al., 1975; Miletto, 1972; Nahunek et al., 1974). Patients with psychotic depression have required larger doses than those with neurotic depression (Gillmer, 1970); as have hospitalised patients compared with outpatients (Krakowski, 1968). In this study, the dose in hospitalised patients was 75 to 200mg initially, 100 to 500mg* maximum and 75 to 500mg* maintenance compared with 75 to 150mg initially, 75 to 300mg maximum, 50 to 200mg maintenance in outpatients. Dosage in the elderly has involved smaller doses initially, with smaller progressive increases; in one study to a maintenance level of 37.5 to 150mg daily (Moser, 1969).

Although a few patients begin to improve during the first week of therapy on a divided dose regimen, the antidepressant effect in most patients generally occurs after 7 to 10 or more days (Ayd, 1969; Bergener and Behrends, 1966; Bukowczyk et al., 1971; Gillmer, 1970; Krakowski, 1968). In a retrospective study, a single daily bedtime dosage regimen seemed to accelerate the onset of antidepressant effect since significant improvement was noted by the end of 1 week compared with 4 weeks with a 4 times a day schedule (Goldberg et al., 1974b). The earlier a beneficial effect occurred, the better the eventual outcome (Ayd, 1969). Doxepin has been used effectively as maintenance therapy for periods of up to 4 to 7 years in patients with manic-depressive psychosis (depressive phase) and has been well tolerated (Ayd, 1975b).

* In the USA, the maximum recommended daily dose is 300mg.

Side-effects are comparable in nature with those reported with other tricyclic antidepressants; the most common being drowsiness, constipation and dry mouth (see section 4). Excessive drowsiness can be overcome by giving the major portion of the daily dose at bedtime (Moser, 1969) or as a single daily dose at bedtime (see section 4.1). It was well tolerated by elderly patients (Ayd, 1969, 1971, 1975b; Moser, 1969; Vitorovic and Zvan, 1970) and by those with cardiovascular disease (Ayd, 1969, 1975b; Schreiber, 1970; Vitorovic and Zvan, 1970), and has been given concurrently with other psychotherapeutic drugs and commonly prescribed medication without evidence of clinically important interaction (see section 6.1). Although it has a lesser effect on the norepinephrine pump mechanism than other tricyclic antidepressants, at daily doses of 200mg or more doxepin can antagonise the action of adrenergic neuron blocking antihypertensive agents such as guanethidine (see section 6.2).

3.2 Comparisons with Other Antidepressants in Depression

A number of controlled comparative trials have been conducted in hospitalised inpatients, outpatients attending hospital clinics and private psychiatric or general practice patients with depression (table I). With a few exceptions the studies involved small numbers of patients in the treatment groups — a general defect of present-day controlled therapeutic drug trials. Thus, in well matched patient populations it has not been possible for investigators to distinguish a statistically significant difference in efficacy between doxepin and amitriptyline or imipramine. Several hundred patients are likely to be needed to show minor differences between drugs expected to produce a similar response rate (Clark and Downie, 1966). In the only study in which a difference between doxepin and amitriptyline (Hackett and Kline, 1969; Hackett et al., 1967) could be detected, the treatment groups were not comparable.

Doxepin, amitriptyline and imipramine can not therefore in scientific terms be considered equal in

efficacy since an adequate number of subjects were not included in the treatment groups to prove real equivalence; an argument previously proposed by Hollister (1974). However, the superiority of doxepin over placebo and the results and response rate obtained with doxepin can not be ignored, particularly since results achieved under conditions of actual clinical practice (section 3.1) are comparable with those in controlled trials and also suggest that doxepin has a profile of activity similar to that of amitriptyline. Doxepin must therefore be considered an active antidepressant. Studies involving a large number of patients and well matched treatment groups will be needed to determine any difference or equivalence in overall efficacy between doxepin and other tricyclic antidepressants.

While a difference in efficacy has not been detected between doxepin and other tricyclics, there has been a consistent trend in many studies for doxepin to be associated with fewer or less troublesome side-effects than amitriptyline or imipramine (table I).

The sedative properties of doxepin have been employed to advantage in depressed patients with sleep disturbances. Improvement in disturbed sleep pattern seems to be better than that achieved with imipramine (Castrogiovanni et al., 1971; Goldberg et al., 1976; Kimura et al., 1975) and comparable with that attained by amitriptyline. A single bed-time dose appears to be more desirable than a divided daily dose regimen in most patients.

3.2.1 Comparison with Amitriptyline in Depression

Studies which have compared doxepin and amitriptyline under double-blind conditions are summarised in table I. All but one failed to detect any difference in efficacy, although a trend for fewer and/or less troublesome side-effects was noted in some studies. In the study which found a significant difference in favour of doxepin over amitriptyline (Hackett et al., 1967; Hackett and Kline, 1969) the treatment groups were not matched; the group treated with amitriptyline comprised a relatively higher proportion of patients with a longer duration of illness and the dosage of amitriptyline was not equivalent.

In the largest trial in general practice, Jones et al. (1972) compared the antidepressant effects of doxepin and amitriptyline in 63 patients with depression. The groups, which were matched for age and severity of symptoms, showed a close parallel throughout the 8-week trial in terms of speed of onset (within the first 2 weeks) and magnitude of response to treatment. No significant difference was apparent in therapeutic efficacy between doxepin and amitriptyline, either on global evaluation or when scored by the Hamilton Depression Rating Scale. More patients experienced side-effects on amitriptyline and 3 patients were transferred to doxepin because of troublesome side-effects, whereas the reverse was not necessary.

In a study involving predominantly inpatients, Bianchi et al. (1971) found doxepin (mean daily dose, 200mg) to be significantly less effective than amitriptyline (mean daily dose, 160mg) at 14 days of treatment, though the drugs were indistinguishable at days 21 and 35 of the trial. Most of the improvement had occurred by the end of 3 weeks of treatment. Although no difference could be detected between the drugs in the group as a whole (table I), patients with endogenous depression tended to respond better to amitriptyline (71% remission or marked improvement) than to doxepin (53%), whereas those with neurotic depression tended to respond better to doxepin (50%) than to amitriptyline (36%). A greater incidence of and more troublesome side-effects (sedation, dry mouth, sweating, postural hypotension) were reported for amitriptyline. Other investigators have also found a trend for doxepin to produce fewer and/or less troublesome side-effects than amitriptyline (Gomez-Martinez, 1968; Grof et al., 1974; Hackett et al., 1967; Jones et al., 1972; Toru et al., 1972). In the study of Grof et al. (1974), involving mainly elderly patients, the frequency of side-effects with amitriptyline (dosage 100 to 350mg daily) was about twice that with doxepin (dosage 150 to 350mg daily) and some symptoms (tachycardia, blurred vision) were associated solely with amitriptyline.

In contrast to the studies of Bianchi et al. (1971) and Toru et al. (1972), which found that amitriptyline was more rapid in onset of antidepressant action than

doxepin, Solis et al. (1970) observed that patient self-rating scores (Zung Scale) were significantly improved at days 7 and 14 of treatment only with doxepin. Amitriptyline showed a statistically significant effect only after the third week of treatment after which both drugs were equally effective.

3.2.2 Comparison with Imipramine in Depression

Comparisons of doxepin with imipramine have generally shown doxepin to produce a lesser incidence of troublesome side-effects. The relative efficacy of the two drugs is indeterminate although the antidepressant effects of doxepin may be slower in onset (Castrogiovanni et al., 1971; Hasan and Akhtar, 1971). One study of single bedtime dosage regimens (Goldberg et al., 1975b; 1976) could not find statistically significant greater overall response with imipramine, but generally the patients treated with imipramine showed slightly more improvement than did those treated with doxepin, the trend for clinical evidence of improvement favouring imipramine (81% imipramine; 69% doxepin marked to moderate improvement). Kimura et al. (1975) in a study involving 191 patients found a similar trend, but suggested that doxepin and imipramine may have different efficacy on particular nosologic types of depression. Although no statistically significant difference could be detected in overall efficacy, doxepin (30 to 150mg daily) on global evaluation tended to be superior to imipramine (30 to 150mg daily) in neurotic depression and imipramine superior to doxepin in endogenous depression (fig. 4). Less difference existed in involutional depression. This difference in endogenous and neurotic depression was most marked in relief of various symptoms up to 3 weeks but tended to decrease gradually from week 4 on.

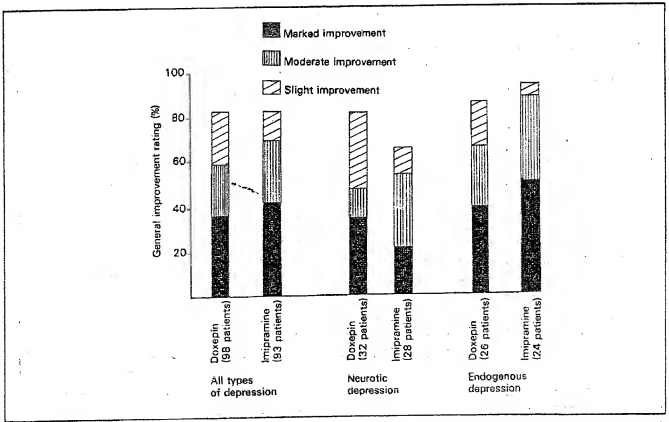


Fig. 4. Patients with depression. Degree of general improvement with doxepin and imipramine and according to nosologic diagnosis (data from Kimura et al. (1975).

Doxepin had a superior effect in relief of disturbed sleep patterns and tended to cause a smaller incidence of side-effects (constipation, sweating, dizziness, tachycardia, micturition disturbances).

Castrogiovanni et al. (1971) gave doxepin or imipramine, in mean daily doses of 222 or 202mg respectively, to 44 hospitalised patients with psychotic depression who were well matched in two groups for age, sex, and type and severity of illness. Both drugs produced significant improvement in Hamilton Depression Scale scores and in the Brief Psychiatric Rating Scale scores, as well as by global clinical evaluation. However, this improvement was statistically significant by day 8 of treatment with imipramine, but only became significant for doxepin at day 16. Doxepin was judged to have a more marked sedative effect than imipramine, as determined by its greater effect on the symptom 'agitation' in the Hamilton Depression Scale. Side-effects were significantly more frequent and severe with imipramine. Withdrawals due to side-effects were necessary in 4 of 26 patients in the imipramine group (cardiovascular 3; tremors 1) but none in the doxepin group, while a further 6 patients (5 on imipramine) withdrew due to rapid worsening of psychotic symptoms.

Hasan and Akhtar (1971), in a study involving smaller body build Pakistani patients, also found doxepin (75mg daily) to cause fewer side-effects than imipramine (75mg daily), but to have a slower onset of antidepressant effect. Of the 33 patients who completed the 5-week trial, 16 received doxepin and 17 took imipramine. A variety of side-effects were reported by 15 of those on imipramine, but only dry mouth and sedation occurred in a total of 5 patients on doxepin. Both drugs produced significant improvement in all the symptoms of the Hamilton Depression Scale over 5 weeks, but imipramine was significantly superior during the first 3 weeks of the trial. Global evaluation at the end of 5 weeks showed that 12 of 16 (75%) patients on doxepin showed marked to moderate improvement (no total remissions) compared with 13 of 17 (76%) patients on imipramine (including 1 remission).

Both Hasan and Akhtar (1971) and Goldberg et al. (1976) found that although there was no statistically significant difference in overall response between imipramine and doxepin, with the exception of sleep disturbances (Goldberg et al., 1976), imipramine had a greater effect on individual target symptoms than did doxepin.

3.2.3 Comparisons with Other Drugs in Depression

In preliminary studies, doxepin has been shown to be superior to opipramol, although in this study the nosologic groups of patients were not well matched (Boysen et al., 1970). In another study, no difference could be detected between doxepin and dothiepin, but doxepin tended to have a more rapid onset of effect and dothiepin tended to cause a smaller incidence of troublesome side-effects (GP Research Group, 1976). Again the treatment groups were not well matched; the group treated with dothiepin containing a relatively higher proportion of patients with a shorter duration of symptoms.

Doxepin achieved a similar response rate (74%) as dibenzepin (76%), but a greater success rate than chlorimipramine (64%) in a group of 121 depressed patients — endogenous (60), neurotic (38), organic (20). Doxepin was considered less effective than dibenzepin or chlorimipramine in improving mood but to be preferred in patients with depression associated with anxiety. Dibenzepin was the most effective drug in inhibited depressives but caused a greater incidence of troublesome side-effects (Nurowska and Welbel, 1973).

3.3 Depression Associated with Sleep Disturbances

Significant improvement in the disturbed sleep patterns of psychoneurotic depressed patients has been shown in most studies, and some investigators have studied this specifically. Thus, doxepin has produced polygraphic changes (electroencephalography; electro-oculography) similar in some respects to those produced by other tricyclic antidepressants (Castogiovanni et al., 1971; Karacan et al., 1975;

1977; Karacan and Williams, 1976). In particular, doxepin has been found to increase total sleep time by reducing sleep latency and/or time awake after sleep onset. It has also produced an increase in stages 3 and 4 sleep. Although it has been reported to reduce REM sleep and produce a REM rebound after drug discontinuation in insomniacs (Kales et al., 1972), it produced either an increase (Castogiovanni et al., 1971) or no significant changes (Karacan et al., 1975; 1977; Karacan and Williams, 1976) in the REM sleep of depressed patients. This inconsistency in findings may reflect differences in the patient populations in 'abnormality' of REM sleep prior to the study or variability of REM sleep during the study. The biological significance of REM sleep is not known, but some investigators believe that depressive illness is associated with REM sleep deprivation and that clinical improvement in depression is associated with increases in REM sleep (Mendels and Hawkins, 1971). Indeed, doxepin has tended to normalise sleep patterns in depressed patients, and improvements in sleep have paralleled improvements in depressive symptomatology (Castogiovanni et al., 1971; Karacan et al., 1976; 1977; Karacan and Williams, 1976). Most changes in sleep patterns occurred within the early phase of drug treatment, but a few were only transitory (Karacan et al., 1975; 1977; Karacan and Williams, 1976).

In a comparative study of tricyclic antidepressants in healthy subjects, Dunleavy et al. (1972) found that 75mg nightly doses of doxepin, imipramine, desipramine and chlorimipramine reduced REM sleep duration, with chlorimipramine being most potent and doxepin the least. This effect lessened during a month of drug administration, and a rebound followed which lasted for a month. Doxepin reduced intra-sleep restlessness, as in the depressed patients, whereas the other antidepressant drugs increased restlessness. These effects did not diminish with time and did not show a rebound.

Most sleep laboratory studies with other tricyclic antidepressants have been conducted in normal subjects or isomniacs, rather than with depressed patients. Whether or not the effects of a tricyclic drug are the same in normal subjects as in depressed patients remains to be determined.

Superior effects on morning feelings of rest after bedtime dosage of 100mg doxepin were shown in a comparison with a 4 times daily dosage regimen by Mendels and Schless (1975) in depressed patients with sleep disturbances. Doxepin also decreased patient awakenings during the night and reduced the time taken to fall asleep, whatever the dosage regimen. Other investigators have confirmed these findings with single bedtime dose regimens in patients with depression associated with anxiety (see section 3.7.3). Single daily dose regimens of psychotherapeutic drugs, particularly tricyclic antidepressants, have many advantages (e.g. Ayd, 1974). Not only has improvement in sleep been observed in depressed patients, but complaints of commonly occurring side-effects (e.g. drowsiness, dizziness, lethargy) have been less troublesome (Goldberg et al., 1974b).

The addition of a hypnotic (flurazepam) to doxepin does not appear to enhance its therapeutic effects in depressed patients with sleep disturbances, thus avoiding the need for an hypnotic at night (Smith and Renshaw, 1974). Sleep disturbances were improved to a similar degree in 35 patients who received a daytime placebo with a single bedtime dose of doxepin (50 to 100mg) and in 34 patients who received doxepin 25 to 50mg twice daily with a bedtime dose of flurazepam (30mg). Clinical evaluation of overall response also showed no significant difference between the groups; with marked to moderate improvement in depressive symptoms in 21/29 patients who completed 4 weeks on doxepin plus a placebo, and in 17/27 patients who completed 4 weeks of treatment with doxepin plus flurazepam.

3.4 Depression in the Elderly

Doxepin is effective and well tolerated by elderly patients with depression (Ayd, 1969, 1971, 1975b; Moser, 1969; Vitorovic and Zvan, 1970), but in 2 studies they tended to respond less favourably than

younger patients (Ayd, 1969; Poeldinger et al., 1966). It can be conveniently given with the major portion or entire dose at bedtime, so avoiding excessive sedation during the day (Ayd, 1975b; Moser, 1969). Treatment should begin with a low dose of 25 to 50mg, but some depressed elderly patients *need* and can tolerate 150 or even 300mg daily if the dose is gradually increased (Charatan, 1975; Chien et al., 1973; Friedel and Raskind, 1975; Raskind et al., 1976).

Most comparative controlled trials in depression have involved groups of patients with a wide age range, but usually with an average age of less than 50 years. One trial involved older patients. Grof et al. (1974) studied 22 patients with an age-range of 29 to 74 years (average 51 years), in whom the antidepressant effects of doxepin 150 to 350mg* daily were indistinguishable over 4 weeks of treatment from those of amitriptyline 100 to 250mg daily (see table I). Doxepin, however, produced fewer side-effects (tachycardia, accommodation difficulties) in this older age group than did amitriptyline, and it was significantly superior in terms of relief of hypochondrial complaints. Another study (Beber and Georgia, 1975), could not distinguish between doxepin oral concentrate (50 to 100mg daily) and amitriptyline capsules (50 to 100mg daily), although patients' préférences favoured doxepin for relief of sleep disturbances.

Elderly patients, including those with cardiovascular disorders, do not seem to have an increased susceptibility to cardiovascular or other toxicity with doxepin (Ayd, 1969, 1971, 1975b; Coleman, 1969; Pitts, 1969), although the usual precautions for use of drugs of this type (e.g. lowered threshold for confusional states, urinary retention, constipation, postural hypotension, Parkinson's syndrome) in the elderly should be observed (Prange, 1973).

* In the USA, the maximum recommended daily dose of doxepin is 300mg and in once-daily schedules the maximum recommended daily dose is 150mg.

3.5 Depression in Patients with Cardiovascular Disease

Doxepin has been used satisfactorily to treat depression in patients with cardiovascular disease, without evidence of significant cardiovascular side-effects (Ayd, 1971, 1975b; Coleman, 1969; Krakowski, 1968; Moser, 1969; Schrieber, 1970; Vitorovic and Zvan, 1970). At a dose of 75mg daily doxepin had no adverse effect on depressed patients recovering from acute myocardial infarction; as determined by monitoring for arrhythmias and increase in central venous pressure. Nor did amitriptyline 75mg perphenazine 6mg affect cardiovascular function in these patients (Coleman, 1969). Tricyclic antidepressants should nevertheless be used cautiously and in low doses in those with myocardial ischaemia.

In long-term studies of maintenance doxepin in patients with cardiovascular disease, Ayd (1975b) observed that only patients taking more than 200mg daily experienced transient tachycardia. Doses below this level appeared to have no adverse cardiovascular effects in standard tests (EKG, pulse rate, blood pressure) carried out periodically during the 6 years or more of doxepin administration. The cardiovascular side-effects of doxepin may, like those of other tricyclic antidepressants, be dose-dependent, although doxepin appears to be considerably less cardiotoxic than amitriptyline, nortriptyline or imipramine in depressed patients (see section 1.2.3). In particular, doxepin produced less marked increases in heart rate and PR interval, and thereby had a lesser effect on intracardiac conduction than the other tricyclic antidepressants tested.

In doses up to 300mg daily, doxepin had no effect on blood pressure of treated hypertensive patients (Ayd, 1975b; Belsasso et al., 1969; Krakowski, 1968). Doxepin has a lesser effect than other tricyclic antidepressants on the norepinephrine pump mechanism and is consequently less potent in inhibiting the action of adrenergic neuron blocking antihypertensive agents such as guanethidine (see sections 1.1.5; 1.2.2). However, at daily doses above 150mg doxepin

can antagonise the antihypertensive effect of guanethidine (see section 6.2).

3.6 Long-Term Use in Depression

A number of depressed patients in various trials have continued to receive doxepin for long periods of time, without any apparent development of toxicity or tolerance to its therapeutic effects. In two studies it has been given for up to 7 years to patients with affective psychoses particularly of the manic-depressive (depressive phase) or schizoaffective type (Ayd, 1971, 1975b; Radmayr, 1976).

Ayd (1971) in an uncontrolled study, reported on 40 chronically depressed patients with manic-depressive (depressive phase) or schizoaffective syndromes, who received maintenance treatment with doxepin for 18 to 41 months. In a subsequent report, he continued to follow 32 of these patients for a further 3 to 4 years (Ayd, 1975b). About half of the patients were elderly, aged between 50 and 75 years, and most of them had one or more physical diseases besides their chronic depression. The more serious of these were cardiovascular or gastrointestinal in nature, together with epilepsy and diabetes. Consequently, many patients were receiving, in addition to doxepin and various antipsychotic drugs, treatment with digitalis, antihypertensives, oral hypoglycaemics, antacids and anticonvulsants. All patients took the entire daily dose of doxepin at bedtime (usually 150mg), except for those aged over 60 years who took half after dinner and the rest at bedtime.

Significant reduction in symptoms was observed in all patients, who were generally able to continue with their daily lives. However, disabling symptoms reappeared whenever doxepin was withdrawn, and the dosage frequently required adjustment at times of increased stress. Dryness of the mouth and constipation were the only side-effects which persisted throughout the study, but all patients gained weight within the first 6 months. Several patients taking more than 200mg daily experienced some transient tachycardia, but there were no other adverse cardiovascular effects (see section 3.5). The drug was well tolerated by those patients with cardiovascular disease and other physical disorders, and there were no adverse interactions with other drugs used. In 2 patients, doxepin 200mg daily had no effect on blood pressure control in those already receiving guanethidine. No significant or persisent laboratory abnormalities were detected during regular estimations of renal and liver function and blood chemistry.

None of the patients in the study had attacks of depression sufficiently severe to necessitate hospitalisation, but all had at one time or another a need to increase their dosage to control re-emergence of symptoms. Intermittent maintenance therapy may be possible in some patients, for the interval between stopping doxepin and the recurrence of affective symptoms varied from a few days to 6 months or more.

3.7 Depression with Associated Anxiety

This group includes those patients diagnosed with predominantly depressive symptoms but in whom significant anxiety was also present, as well as those patients diagnosed as mixed depression-anxiety syndrome in whom neither symptom was considered to predominate; a common complaint among psychiatric patients. It also includes studies which included mixed populations of depressed and depressed-anxious patients, but which did not express results separately for each group.

3.7.1 Uncontrolled Studies in Depression with Anxiety

Experience from uncontrolled trials suggests that doxepin can produce marked to moderate improvement in about 60% of patients (Pitts, 1969), including patients who had failed to respond adequately to other agents (Ciurezu and Timofte, 1974; Krakowski, 1969; Lang, 1970; Pitts, 1969) and patients with severe affective illness (Krakowski, 1969; Pereira and Lipke, 1970). Doxepin was well tolerated and effective in decreasing agitation and lessening apathy in 24 elderly patients treated with 75 to 150mg daily over a period of 6 months (Spalding, 1976). Bohlau et al.

Table II. Summary of results of double-blind comparative trials in patients with predominantly depression associated with anxiety or with depression-anxiety syndrome or mixed populations

Author	Diagnosis	Population	Groups well matched[1]	Daily dosage doxepin (D)	Daily dosage other drug	Duration	Efficacy[2] (see also text)	Onset of response	Side-effects (see also text)	Response rate (%)[3] doxepin ++	doxepin +	other ++	other +
Comparison with chlordiazepoxide (C) or placebo (Pl)													
Goldstein et al. (1973)	Depression-anxiety	Outpts (121)	Yes	50-150mg	20-60mgC	4w	D > C C = Pl	—	D = C	...	...	...	...
Montgomery et al. (1970)	Reactive depression (9) Depression-anxiety (15) Anxiety (16) Other (1)	GP (41)	No (D)	20-90mg (30mg)	20-90mgC (30mg)	4w	D > C	D > C	D > C	64	9	42	5
Comparison with amitriptyline (A) + chlordiazepoxide (C)													
Ebie (1974)	Depression-anxiety	Outpts (64)	7Yes	30-75mg	37.5-75mgA 15-30mgC	8w	D = A-C D > Pl	—	D = A-C	...	86	...	81
Laffranchini (1971)	Depression with anxiety	Outpts (51)	Yes	30-70mg	37.5-75mgA 15-30mgC	11-56d	D > A-C	—	D = A-C	...	...	...	...
Comparison with amitriptyline (A) or placebo (Pl)													
Haider (1971)	Depression with anxiety	Outpts and Inpts (102)	Yes	75-150mg	75-150mgA	3w	D = A	—	D > A	54	29	40	44
Kiev (1974)	Neurotic depression (47) Depression-anxiety (40) Other (2)	Outpts (89)	Yes	75-150mg (102mg)	50-225mgA (110mg)	4-12w	D = A A = Pl D > Pl	D = A	D = A	32	29	10	33
Querol (1970)	Depression with anxiety	Outpts (63)	Yes	25-150mg	25-150mgA	4w	D > A	D > A	D = A	71	...	50	...
Sangor (1969a,b)	Depression-anxiety in allergic skin disorders	Outpts (32)	No (D)	50-100mg	50-75mgA	6w	D > A	D = A	D = A	19	56	0	38

Silva and Siques (1972)	Depression-anxiety (31) Depressive reaction (9) Depressive personality (16)	Outpts (56)	?Yes	25-100mg	25-100mg	6w	D = A D > A (anxiety)	D < A (depression) D > A (anxiety)	D = A	21	48	15	52
Comparison with amitriptyline (A) + perphenazine (P) or placebo (Pl)													
Coleman (1969)	Depression-anxiety with organic illness	Outpts and Inpts (40)	No (A-P)	75mg	75mgA 6mgP	18-85d	D = A-P D > Pl	—	D = A-P	21	43	36	27
Goldstein and Pinosky (1969)	Depression-anxiety Depression Anxiety (psychoneurotic)	Outpts (26)	—	75-300mg	75-300mgA 6-24mgP	4w	D = A-P	D > A-P	D < A-P	45	36	40	3
Krakowski (1969)	Depression with anxiety (neurotic)	Outpts and Inpts (36)	No (D)	150-300mg	150-300mgA 12-24mgP	4-12w	D = A-P (clinical) D > A-P (rating scale)	D > A-P	D < A-P	29	35	16	47
Naftulin and Ware (1972)	Depression-anxiety Depression Anxiety	Outpts (40)	—	75mg	75mgA 6mgP	5w	D = A-P	D > A-P (anxiety) D < A-P (depression)	D = A-P	6	28	17	11
Rickels et al. (1972)	Depression-anxiety (72) Depression (17) Other (11)	Outpts and GP (100)	Yes	75-150mg	75-150mgA 6-12mgP	4w	D > A-P D < A-P (see text)	D = A-P	D > A-P D < A-P (dropouts)	...	...	...	...

1 Population distribution favoured efficacy for drug indicated in parentheses, usually because of less patients with greater duration or severity of illness, and sometimes because of unequal distribution of patient types or previous treatment, etc. An elipsis (...) signifies insufficient information or not clear whether groups reasonably well matched. A dash (—) signifies no appropriate data provided. See also text.

2 Efficacy overall on basis of clinical (global) and psychiatric symptom rating scales. In many cases trends towards differences emerged between the study drugs. See text for explanation.

3 Response rate in terms of global clinical evaluation only. + + = remission or marked improvement; + = moderate improvement; (—) = no clinical assessment of results given; (...) = results not expressed as percentage. A figure only in + column signifies marked plus moderate improvement. See also text.

(1972) also found doxepin (20mg daily) to be effective and well tolerated in the elderly. The effect of doxepin on anxiety symptoms appears to become manifest earlier (within 5 to 6 days) than its effect on depressive symptoms which is seen after 7 to 10 or more days (Ciurezu and Timofte, 1974; DuBois, 1969; Pereira and Lipke, 1970). Patients with psychotic illness seem to require larger doses (50 to 150mg daily) than those with neurotic illness in whom 50 to 75mg daily seemed to be the optimum dose (Ciurezu and Timofte, 1974) but to respond as favourably (Pitts, 1969). In a group of patients who had failed to respond to other agents, the dosage range was 50 to 300mg daily (mean maximum dosage 225mg; maintenance 175mg), with 1 patient requiring 400 to 500* (Krakowski, 1969). In divided dosage regimens, giving the larger portion of the dosage at bedtime proved useful in those with sleep disturbances (Dubois, 1969).

3.7.2 Comparisons with Other Drugs in Depression with Anxiety

Doxepin has been compared in double-blind trials with amitriptyline or chlordiazepoxide alone and with fixed combinations of amitriptyline-perphenazine and amitriptyline-chlordiazepoxide (table II), and has been shown to be superior to a placebo (Coleman, 1969; Ebie, 1974; Hollanda et al., 1970; Kiev, 1974).

Comparison with Chlordiazepoxide or Amitriptyline-Chlordiazepoxide

In those studies involving matched treatment groups, doxepin was superior to amitriptyline-chlordiazepoxide (Laffranchini, 1971) in one study, although another study (Ebie, 1974) could not detect a significant difference between doxepin and the amitriptyline-chlordiazepoxide combination. Doxepin, as to be expected, was superior to chlordiazepoxide alone (Goldstein et al., 1973; Gonzalez, 1967; Israel et al., 1970; Montgomery et al., 1970).

* In the USA, the maximum recommended daily dose is 300mg.

Comparison with Amitriptyline-Perphenazine

Comparisons of doxepin with amitriptyline-perphenazine have failed to detect a statistically significant difference between the two drugs (Coleman, 1969; Goldstein and Pinosky, 1969; Krakowski, 1969; Naftulin and Ware, 1972), although Rickels et al. (1972) in a study involving larger numbers of patients, found amitriptyline-perphenazine to be slightly more effective than doxepin. Side-effects do, however, appear to be less troublesome with doxepin than amitriptyline-perphenazine (Goldstein and Pinosky, 1969; Krakowski, 1969; Rickels et al., 1972) and in two studies, doxepin appeared to have a more rapid onset of effect than amitriptyline-perphenazine (Goldstein and Pinosky, 1969; Krakowski, 1969).

In the studies of Goldstein and Pinosky (1969) and Krakowski (1969), doxepin and the amitriptyline-perphenazine combination appeared to produce a differential pattern of improvement, not only in terms of the rate of overall response on physician ratings but also in terms of the four factors of the Hamilton Depression Scale. Patients treated with doxepin responded favourably in all four factors early in treatment, whereas those receiving amitriptyline/perphenazine only showed improvement in retarded depression during the first week with slower improvement in the other factors (anxiety, somatisation and agitated depression). In contrast, Naftulin and Ware (1972) found doxepin to have a more rapid effect than amitriptyline-perphenazine on symptoms of anxiety, while amitriptyline-perphenazine had a more rapid effect on depressive symptoms. However, no information was given as to whether the two treatment groups were well matched.

Rickels and colleagues (1972) studied 100 outpatients allocated at random to doxepin (50) or amitriptyline-perphenazine (50) groups. The groups were well matched (Rickels pers. comm.). Patients received either doxepin 75 to 150mg or the same dose of amitriptyline plus 6 to 12mg perphenazine for 4 to 6 weeks. Relatively few statistically significant differences were found between the treatment groups, despite the use of numerous objective and subjective

methods of analysis. The main drug effect in terms of trend for overall improvement was in favour of the combination. Patients attending psychiatric clinics tended to respond better to doxepin, while general practice and private psychiatric practice patients improved most with amitriptyline-perphenazine. The combination produced greater improvement in patients with high levels of depression, while doxepin produced a more favourable response in those with low levels of depression. Doxepin was also more effective in lower than in higher social class patients. Side-effects were more common in the doxepin group, but patients on doxepin withdrew less frequently than those on amitriptyline-perphenazine.

Comparison with Amitriptyline

In general, the trend is for doxepin to be superior to amitriptyline. In a comparison with amitriptyline alone in patients with anxiety and depression associated with allergic dermatologic conditions, although doxepin was shown to be of statistically significant superior efficacy (Sanger, 1969a,b), the patients in the amitriptyline group had experienced a much longer duration of illness. In another study (Silva and Siques, 1972) in patients with mixed depression-anxiety, doxepin and amitriptyline produced a similar improvement in depressive symptoms (doxepin 71.5%; amitriptyline 75% marked improvement) but doxepin had a greater effect on the anxiety component (doxepin 81%; amitriptyline 63% marked improvement). Amitriptyline produced a more rapid response on depression and doxepin on anxiety symptoms. Side-effects were similar in both groups. Haider (1971) also found doxepin to be superior to amitriptyline in relief of agitation and anxiety, and although not statistically significant, to produce a greater improvement in more patients. Doxepin caused a higher incidence of paraesthesia, but in no case did this necessitate withdrawal of treatment.

In contrast, although Kiev (1974) could not find a statistically significant difference between doxepin and amitriptyline in a mixed population of 59 adult patients with neurotic depression and depression-anxiety attending an outpatient crisis intervention clinic, the trend favoured doxepin for relief of both anxiety and depression, particularly depression. Moreover, a larger percentage of patients responded to doxepin, as assessed by both global clinical evaluation (doxepin 61%, amitriptyline 43% marked to moderate improvement) and the Hamilton Depression Scale (doxepin 51%, amitriptyline 40% improvement), and only doxepin was statistically significantly superior to the placebo control (fig. 5). The incidence of side-effects was similar with both antidepressants.

Comparison with Thioridazine

No difference in efficacy could be detected between doxepin (75 to 150mg daily) and thioridazine (75 to 150mg daily) in a group of 53 patients with anxiety and depression, but thioridazine produced more troublesome side-effects, particularly ejaculatory impotence in males. Five patients in the thioridazine group, but none in the doxepin group, dropped out because of side-effects (Glick, 1973).

3.7.3 Depression/Anxiety Associated with Sleep Disturbances

Goldberg and Finnerty (1972b; Goldberg et al., 1974b) noted that doxepin (50 to 300mg* daily),

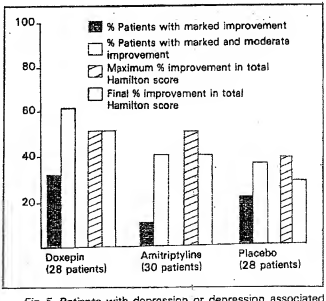


Fig. 5. Patients with depression or depression associated with anxiety. Proportion of patients with moderate and/or marked improvement by global evaluation, and the maximum and final percentage reduction in total Hamilton Depression Scores (data from Kiev, 1974).

Table III. Summary of double-blind comparative trials in patients with depression or depression/anxiety associated with chronic alcoholism

Author	Diagnosis	Population	Groups well matched[1]	Daily dosage doxepin (D)	Daily dosage other drug[2]	Duration	Efficacy[3] (see also text)	Onset of response	Side-effects (see also text)	Response rate (%)[4]			
										doxepin		other	
										+ +	+	+ +	+
Butterworth and Watts (1971)	Depression-anxiety (neurotic)	Inpts (39)	No (Di)	75mg	15mgDi	3w	D > Di	—	D = Di	10	25	11	16
Gallant et al. (1969)	Depression-anxiety Depression Anxiety (neurotic)	Inpts (100)	...	75mgD_1 150mgD_2	15mgDi	3w	D_2 = Di > Pl[5] D_1 = Pl	D_2 > Di	D = Di	...	75	...	71
Knott et al. (1972)	Depression-anxiety (63) Depression (40) Anxiety (17)	? (120)	—	75mg	75mgA 6mgP	8w	D > A-P	D > A-P	D = A-P	25	40	8	30

1 Population distribution favoured efficacy for drug indicated in parentheses, usually because of less patients with greater duration or severity of illness, and sometimes because of unequal distribution of patient types or previous treatment, etc. An elipsis (...) signifies insufficient information or not clear whether groups reasonably well matched. A dash (—) signifies no appropriate data provided. See also text.

2 Abbreviations: Di = diazepam; A = amitriptyline; P = perphenazine; Pl = placebo.

3 Efficacy overall on basis of clinical (global) and psychiatric symptom rating scales. In many cases trends towards differences emerged between the study drugs. See text for explanation.

4 Response rate in terms of global clinical evaluation only. + + = remission or marked improvement; + = moderate improvement; (—) = no clinical assessment of results given; (...) = results not expressed as percentage. A figure only in + column signifies marked plus moderate improvement. See also text.

5 At end of first week.

compared with placebo, enabled patients to fall asleep more easily and also produced a greater feeling of rest upon morning awakening. These effects were confirmed in a later retrospective by the same group (Goldberg and Finnerty, 1973; Goldberg et al., 1974a), which showed that there was no significant difference between once daily (at bedtime) or 3 times daily dosage regimens of doxepin 50 to 300mg* daily in terms of overall improvement in depressive state, though bedtime dosage was significantly better against insomnia. No patient in either regimen had to be withdrawn because of side-effects. In comparison with another group of patients with depression associated with anxiety who were given doxepin in a 3 times daily schedule, single bedtime dosage seemed to accelerate the onset of antidepressant effect; since a significant improvement in depressive symptoms was noted by the end of the first week of treatment with bedtime dosage compared with 4 weeks with the divided daily dose schedule (Goldberg et al., 1974b). Other advantages of a single bedtime dose regimen are discussed in section 3.3.

3.8 Depression and Depression/Anxiety Associated with Alcoholism and Other Drug Abuse

The most frequently encountered emotional symptoms in chronic alcoholic patients are depression and anxiety, frequently in combination. Doxepin would appear to have a useful *short-term adjunctive role* in the overall management of chronic alcoholic patients; relief of symptoms of depression and anxiety helping the patient relate to a comprehensive treatment and rehabilitation programme.

Double-blind comparative studies (table III) have shown doxepin to be superior in efficacy to placebo (Gallant et al., 1969; Knott et al., 1972) or a combination of amitriptyline-perphenazine (Knott et al., 1972). In one study (Gallant et al., 1969), no overall difference in efficacy could be detected between diazepam and doxepin, but in another (Butterworth and Watts, 1971) the trend in response favoured doxepin. However, doxepin had a more rapid onset of effect than diazepam (Gallant et al., 1969) and also amitriptyline-perphenazine (Knott et al., 1972). Only in the study of Gallant et al. (1969) were the treatment groups said to be reasonably well matched.

3.8.1 Comparison with Amitriptyline-Perphenazine in Alcoholism

The study of Knott et al. (1972) involved 120 chronic alcoholic patients with symptoms of depression and anxiety. Doxepin 75mg daily, proved to be significantly more effective than either a placebo or a combination of amitriptyline 75mg and perphenazine 6mg daily. Doxepin had a more rapid onset of effect than the combination treatment or placebo, and after 8 weeks marked to moderate clinical evidence of improvement was apparent in more doxepin-treated patients than in the other groups (table III). The incidence of side-effects was similar in the drug-treated groups, although drowsiness was more common with doxepin and dry mouth more common with amitriptyline-perphenazine.

3.8.2 Comparison with Diazepam in Alcoholism

In a similar population of 100 patients with depression and anxiety, Gallant et al. (1969) studied the effects of two dosages of doxepin as well as diazepam and placebo. According to global (clinical) ratings, diazepam 15mg or doxepin 150mg daily were superior to placebo or doxepin 75mg daily over a 3 week period (table III), although there were no statistically significant differences between treatments according to other rating methods (NIMH Self-Rating Scale and NIMH Symptom Rating Scale). At the end of 1 week of treatment, all drug treatments on global ratings were significantly superior to placebo, an important finding in view of the usually rapid remission of anxiety and depression in alcoholic patients. Doxepin appeared to be more rapid in action than diazepam, since 71% of doxepin-treated patients showed moderate to marked clinical improvement after 1 week, whereas the same percentage of

* In the USA, the maximum recommended daily dose is 300mg.

Table IV. Summary of results of double-blind comparative trials in depressed patients with associated organic disease or functional symptoms.

Author	Diagnosis	Population	Groups well matched[1]	Daily dosage doxepin (D)	Daily dosage other drug[2]	Duration	Efficacy[3] (see also text)	Onset of response	Side-effects (see also text)	Response rate (%)[4]			
										doxepin		other	
										+ +	+	+ +	+
Chaplan (1975)	Depression-anxiety (60)	Outpts with functional gastrointestinal disturbances	Yes	50-150mg	25-250mgA 2-12mgP	4w	D > A-P	D > A-P	D < A-P	14	55	3	45
Coleman (1969)	Depression-anxiety with organic illness (40)	Inpts and outpts with mainly cardiovascular (17) gastrointestinal (8) or bone disease (6)	No (A-P)	75mg	75mgA 6mgP	18-85d	D = A-P D > Pl	—	D = A-P	21	43	36	27
Sanger (1969a,b)	Depression-anxiety in allergic skin disorders (32)	Outpts with allergic skin disease	No (D)	50-100mg	50-75mgA	6w	D > A	D = A	D = A	19	56	0	38
Traitz et al. (1976)	Neurotic depression (60)	Outpts with functional gastrointestinal disturbance	—	25-150mg (72mg)	25-150mgA (72mg)	4w	D = A	—	D = A	60	10	47	21

1 Population distribution favoured efficacy for drug indicated in parentheses, usually because of less patients with greater duration or severity of illness, and sometimes because of unequal distribution of patient types or previous treatment, etc. An elipsis (...) signifies insufficient information or not clear whether groups reasonably well matched. A dash (—) signifies no appropriate data provided. See also text.

2 Abbreviations: A = amitriptyline; P = perphenazine; Pl = placebo.

3 Efficacy overall on basis of clinical (global) and psychiatric symptom rating scales. In many cases trends towards differences emerged between the study drugs. See text for explanation.

4 Response rate in terms of global clinical evaluation only. + + = remission or marked improvement; + = moderate improvement; (—) = no clinical assessment of results given; (...) = results not expressed as percentage. A figure only in + column signifies marked plus moderate improvement. See also text.

diazepam-treated patients showed a similar degree of improvement only after 3 weeks of treatment. Side-effects were mild to moderate and included drowsiness in 14 of 15 patients from each drug group and in 10 of the placebos. Dry mouth, more frequent in the doxepin groups, appeared to be dose-related.

Doxepin was shown to be superior to diazepam in a study involving 39 alcoholic patients with depression and anxiety, with symptoms of anxiety predominant (Butterworth and Watts, 1971). BPRS ratings after 3 weeks of doxepin treatment (75mg daily) showed statistically significant differences over diazepam (15mg daily) in terms of relief of anxiety, depressed mood, somatisation, guilt and tension, although there were no significant differences between treatments on the patient-rated Zung Scale. Global ratings were more improved in the doxepin group (table III). Both drugs were well tolerated.

3.8.3 Depression/Anxiety in Heroin Addicts

Preliminary studies suggest that doxepin may have a useful adjunctive role in relief of depression and anxiety in heroin addicts undergoing a methadone maintenance programme (Dufficy, 1973; Spensley, 1976; Woody et al., 1975). In a placebo-controlled study, relief of depression by doxepin appeared to reduce the self-reported consumption of amphetamines. The reported use of alcohol and barbiturates also tended to be less in the doxepin group (Woody et al., 1975). Relief of symptoms of depression and anxiety seemed to make the patients less restless and better able to participate in other areas of the treatment and rehabilitation programme (Dufficy 1973; Woody et al., 1975). These promising preliminary findings warrant a further more definitive study of doxepin in this difficult treatment area.

3.9 Depression and Depression/Anxiety in Patients with Organic Disease or Functional Disorders Associated with Depression

This group includes patients with depression or depression and anxiety associated with organic disease (e.g. cardiovascular, gastrointestinal, allergic) and those with prominent somatic complaints, usually experienced as symptoms of depressive illness (table IV). Doxepin has been shown to be superior to a placebo in such patients (Coleman, 1969; Forsen, 1975; Rapado, 1969) and to have a striking effect on relief of sleep disturbances (Chaplan, 1975; Forsen, 1975; Rapado, 1969). In studies involving well matched treatment groups, doxepin was superior to amitriptyline-perphenazine in one study involving patients with functional gastrointestinal symptoms (Chaplan, 1975), but it could not be distinguished from amitriptyline alone in another study in patients with functional gastrointestinal disturbances (Traitz et al., 1976) nor from amitriptyline-perphenazine in patients with various organic diseases, predominantly cardiovascular disease (Coleman, 1969). Doxepin does however, appear to produce greater improvement in associated gastrointestinal complaints than amitriptyline-perphenazine (Chaplan, 1975) or amitriptyline (Traitz et al., 1976). Although doxepin was superior to amitriptyline in patients with allergic skin disease, the amitriptyline group had a longer average duration of illness (Sanger, 1969a,b). Clinical experience with doxepin in depressed patients with cardiovascular disease is discussed in section 3.5.

3.9.1 Depression in Patients with Functional Disturbances

In patients with functional gastrointestinal symptoms Chaplan (1975) observed that doxepin (50 to 150mg daily) was consistently superior to amitriptyline (25 to 150mg) plus perphenazine (2 to 12mg), both in relieving symptoms of depression and anxiety and in providing a greater degree of relief from associated gastrointestinal complaints. The predominant symptom of anorexia was relieved in 10 of 14 (71%) patients receiving doxepin compared with only 5 of 14 (36%) of those on the combination; belching was abolished in 6 of 11 (55%) and 7 of 14 (50%) patients respectively. Other gastrointestinal complaints occurred in only a few patients, but were consistently alleviated by doxepin to a greater extent than by amitriptyline-perphenazine. Marked to moderate improvement in depressive-anxious symptomatology

in general was observed in 69% of doxepin patients but in only 48% of those on the combination. Traitz et al. (1976) have confirmed the effectiveness of tricyclic antidepressants in depressed patients with gastrointestinal symptoms, but doxepin 75 to 150mg daily was indistinguishable over 4 weeks from amitriptyline 75 to 150mg; doxepin producing marked to moderate improvement in global ratings in 70% of patients and amitriptyline in 68%; as assessed by a psychiatrist and in 77% and 76% as assessed by a gastroenterologist or generalist. Doxepin tended to produce improvement in gastrointestinal symptoms in more patients (83%) than did amitriptyline (67%). Side-effects were similar in both groups.

3.9.2 Depression in Patients with Chronic Pain

Tricyclic antidepressants also have a useful role in relief of depressive overtones in patients with chronic pain (Hart, 1976). In a placebo-controlled study, Evans et al. (1973) found that doxepin 150mg daily achieved a 70% reduction in analgesic consumption in a group of patients with chronic pain due to bone and joint disease or decubitus ulcers. Improvement in depression in this study appeared to be unrelated to a decrease in analgesic use. Reduction in analgesic use was not confined to those whose mood benefited. The reason for this is not clear (see also section 1.1.7).

3.9.3 Depression in Menopausal Patients

In menopausal patients not receiving oestrogen therapy, doxepin (10 to 125mg daily), proved statistically superior to a placebo in relief of depression and anxiety and sleep disturbances (Forsen, 1975). It also had a lesser effect on relief of climacteric symptoms (flushing, sweating, vertigo, palpitations). Blaine (1975) confirmed these findings in a comparison of doxepin (25 to 150mg daily) and amitriptyline (25 to 150mg daily) in menopausal patients who were receiving oestrogen replacement therapy. A difference in efficacy could not be detected between amitriptyline and doxepin, but there was a trend for doxepin to have a more favourable effect on sleep disturbances. The treatment groups in this study were not well matched but favoured amitriptyline; those in the doxepin group had a longer duration of illness and there were also more patients with psychotic depression and less with neurotic depression in the doxepin group. These preliminary studies suggest that before prescribing any therapy in menopausal patients, apart from assessing the need for treatment, the role and importance of both the physiologic and psychologic factors must be carefully analysed and evaluated.

3.9.4 Sexual Dysfunction in Depressed Patients

Doxepin (100 to 200mg at bedtime) has also been used in males and females to treat complaints of sexual dysfunction experienced as symptoms of depressive illness (e.g. lowered libido, secondary impotence, situational orgasmic dysfunction). Improvement in depressive symptoms was accompanied by reduced complaints of sexual dysfunction (Renshaw, 1975).

3.10 Anxiety

Little published clinical experience is available from uncontrolled trials, although early reports did suggest the antianxiety properties of doxepin (Pitts, 1969; Simeon et al., 1969), which were subsequently confirmed in placebo-controlled trials (Fielding et al., 1969a,b; Gomide, 1969; Kasich, 1969a,b; Pitts, 1969; Souza, 1971). In comparative trials involving small numbers of patients, doxepin has been compared with chlordiazepoxide or diazepam in nearly all studies. In well designed studies, no difference in efficacy has been detected between doxepin and chlordiazepoxide or diazepam, and side-effects have occurred with much the same incidence and severity (table V). As with trials in depression (section 3.2), much larger numbers of patients will be needed to detect any minor differences in efficacy between two active drugs.

It is possible that a number of the patients in this group, even when given an anxiety diagnosis, were really also depressed since the investigator knew that a tricyclic antidepressant drug was being tested. Thus,

in a recent study (Downing and Rickels, 1974), those patients assigned to trials with tricyclic antidepressants who were given a 'mixed anxiety-depression' diagnosis, were more depressed than anxious, while those patients assigned a 'mixed anxiety-depression' diagnosis who were included in studies with benzodiazepines were always more anxious than depressed.

3.10.1 Comparison with Chlordiazepoxide in Anxiety

In a study involving 36 outpatients, Smith (1971) found doxepin 150mg daily to have a more rapid onset of action (within 2 weeks) than 34mg daily chlordiazepoxide (3 weeks). However, the chlordiazepoxide group displayed illness of longer duration, and possibly a lower comparable dosage, although the groups were otherwise matched for sex, age, severity of illness and type of previous treatment. Hamilton Anxiety Scores were reduced to a similar degree by both treatments, and there was no difference between overall rates of improvement. Side-effects tended to be more common in the doxepin group, but all were mild and did not constitute a problem. McLaughlin (1969) could find no difference between doxepin (75 to 150mg daily) and chlordiazepoxide (20 to 25mg daily) over 8 weeks in terms of global evaluation or Hamilton Anxiety Scale scores. Marked to moderate improvement occurred in about 75% of patients in each treatment group; however, those in the doxepin group had a somewhat longer duration of illness. In a study involving anxious outpatients and inpatients with gastrointestinal disease (Hecht, 1969), chlordiazepoxide tended to produce greater improvement and less troublesome side-effects (possible because doxepin dosage was increased too rapidly). On the other hand, Krasner (1971) found that doxepin tended to produce a greater and more rapid response than chlordiazepoxide in general practice patients with an anxiety state. Side-effects were mild and similar in both groups.

There is a suggestion that *in*patients may benefit more from chlordiazepoxide, while *out*patients may benefit more from doxepin. A comparative study in 50 psychoneurotic patients (Sterlin et al., 1972b) showed that both drugs produced a significant overall improvement within the 4-week trial period, as measured by both clinical impression and several psychiatric rating scales. Improvement occurred to some degree in 14 of 25 patients on doxepin, and in 17 of 25 on chlordiazepoxide. When the patient populations were analysed separately (Sterlin et al., 1970, 1971b; 1972b), it was found that neither drug produced notable overall improvement in the ratings of psychoneurotic inpatients within 4 weeks, but both produced improvement in outpatients (doxepin in all 8 patients; chlordiazepoxide in 8 of 11 patients). Dosage of the drugs used to achieve a response also differed — inpatients (doxepin 75 to 300mg daily; chlordiazepoxide 30 to 120mg daily) and outpatients (doxepin 75 to 150mg daily; chlordiazepoxide 30 to 60mg daily). Despite the lack of significant improvement in inpatients, they responded somewhat better to chlordiazepoxide, particularly in respect to changes in symptoms of anxiety and depressive mood, while outpatients showed a better response to doxepin in terms of obsessive-compulsive-phobic manifestations and depressive retardation. There was also a suggestion that doxepin may have a more favourable effect than chlordiazepoxide in outpatients with anxiety associated with depression (Beaubien et al., 1970), a trend supported by other comparative studies (see section 3.11).

3.10.2 Comparison with Diazepam in Anxiety

In a multicentre trial involving 55 patients in general practice (Jones et al., 1972), no statistical difference could be detected between doxepin 25 to 150mg daily and diazepam 5 to 45mg daily. However, more patients on doxepin discontinued treatment because of lack of adequate effect and more doctors favoured continuing diazepam after completion of the trial. Minor side-effects occurred in more patients on doxepin. On the other hand, exactly the opposite trend was observed in another study (Ban, 1976). Although there was no statistically significant overall difference between doxepin 50 to 150mg daily and diazepam 10 to 30mg daily in outpatients attend-

Table. V. Summary of double-blind controlled comparative trials in anxiety

Author	Diagnosis	Population	Groups well matched[1]	Daily dosage doxepin (D)	Daily dosage other drugs	Duration	Efficacy[2] (see also text)	Onset of response	Side-effects (see also text)	Response rate (%)[3]			
										doxepin		other	
										+ +	+	+ +	+
Comparisons with chlordiazepoxide (C) or placebo (Pl)													
Bacal et al. (1969)	Psychoneurosis with cardiovascular symptomatology	? (34)	—	75-150mg	30-60mgC	4w	D = C D > Pl	—	D > C	...	...	...	...
Beaubien et al. (1970)	Psychoneurosis	Outpts (30)	No (D)	75-150mg	30-60mgC	4w	D = C D > C (depression)	—	D = C	—		—	
Hecht (1969)	Anxiety assoc gastrointestinal disease	Outpts and Inpts (29)	—	30mg	15mgC		D < C	—	D > C	27	13	54	23
Krasner (1971)	Anxiety state	GP (30)	No (C)	20-60mg	20-60mgC	4w	D > C	D > C	D < C	58	33	40	27
McLaughlin (1969)	Psychoneurotic anxiety (11) Obsessive compulsive reaction (10) Other (3)	Outpts (24)	No (D)	75-150mg	20-25mgC	8w	D = C	—	D = C	42	25	25	33
Smith (1971)	Psychoneurotic anxiety	Outpts (36)	No (D)	150mg	30mgC	6w	D = C	D > C	D > C	0	53	0	37
Sterlin et al. (1970)	Psychoneurosis	Outpts (30)	—	75-150mg	30-60mgC	4w	D = C	—	D = C	50[4]	25[4]	9[4]	55[4]
Sterlin et al. (1971)	Psychoneurosis	Inpts (20)	—	75-300mg	30-120mgC	4w	D = C	—	D = C	...[4]	40[4]	...[4]	60[4]
Comparisons with diazepam (Di) or placebo (Pl)													
Alix (1969)	Anxiety/agitation assoc cardiac disease or functional cardiac disturbances	Outpts (30)	—	? 30mg	6mgDi	2w	D = Di	—	D > Di	...	75	...	75

Ban (1976)	Psychoneurosis	Outpts (40)	—	50–150mg	10–30mgDi	4w	D = Di	—	D < Di	18	47	6	22
Chaudhry et al. (1970)	Psychoneurosis	Outpts (40)	—	75–150mg	15–30mgDi	4w	D > Di D > Pl	D = Di	D = Di	69	31	54	31
Fielding et al. (1969a,b)	Persistent anxiety	Outpts (12)	—	75mg 150mg	15mgDi 30mgDi	3w	D = Di D > Pl	—	—	...		...	
Jones et al. (1972)	Anxiety	GP (55)	Yes	25–150mg	5–45mgDi	4w	D = Di	D = Di	D > Di	64	...	70	...
Kasich (1969)	Marked anxiety associated with gastrointestinal disease	Outpts (60)	Yes	75–200mg	10–20mgDi	4w	D = Di > Pl	D = Di	D < Di	55	15	70	20

1 Population distribution favoured efficacy for drug indicated in parentheses, usually because of less patients with greater duration or severity of illness, and sometimes because of unequal distribution of patient types or previous treatment, etc. An elipsis (...) signifies insufficient information or not clear whether groups reasonably well matched. A dash (—) signifies no appropriate data provided. See also text.

2 Efficacy overall on basis of clinical (global) and psychiatric symptom rating scales. In many cases trends towards differences emerged between the study drugs. See text for explanation.

3 Response rate in terms of global clinical evaluation only. + + = remission or marked improvement; + = moderate improvement; (—) = no clinical assessment of results given; (...) = results not expressed as percentage. A figure only in + column signifies marked plus moderate improvement. See also text.

4 See text for explanation of differential response between inpatients and outpatients.

ing a psychiatric clinic, more in the doxepin group achieved a marked improvement (11/20) on clinical assessment than in the diazepam group (5/21) and side-effects tended to be more frequent and severe in those on diazepam. Fielding et al. (1969a,b) found doxepin 150mg daily to produce greater improvement than 75mg daily, but in the 6 patients studied to be indistinguishable from diazepam 15 and 30mg daily.

Two studies have compared doxepin and diazepam in patients with anxiety associated with organic disease but again with the small number of patients involved no significant difference could be detected between the drugs. Thus no difference in efficacy emerged between doxepin 75 to 100mg daily and diazepam 10 to 20mg daily in 60 patients with marked anxiety symptoms associated with gastrointestinal disease, although diazepam produced a higher incidence of drowsiness (Kasich, 1969a,b). Response to doxepin was rapid; occurring within a week. The most common target symptoms to respond to doxepin were anxiety, tension and insomnia. In patients with anxiety associated with cardiovascular disease (acute myocardial infarction, arrhythmias), both doxepin 75mg daily and diazepam 6mg daily produced significant improvement in 75% of cases. Doxepin, however, appeared to be more effective in patients with severe agitation and at this dosage caused a greater incidence of drowsiness. No adverse cardiovascular effects were reported. Reduction of the dose of doxepin to 50mg daily in a subsequent series of patients achieved a similar degree of favourable response without evidence of excessive daytime drowsiness (Alix, 1969).

3.10.3 Comparisons with Other Drugs in Anxiety

In one study involving 40 adolescent outpatients (Mises and Moniot, 1971), doxepin 30 to 60mg daily produced a similar favourable response to medazepam 10 to 20mg daily, but doxepin had a more rapid onset of effect and caused fewer side-effects (drowsiness, 'overactivity'). On the other hand, lorazepam, another new benzodiazepine derivative, in a dose of 3mg daily was better tolerated than doxepin 75mg daily. Both drugs achieved a similar response in the 46 outpatients studied (Haslam, 1974). No conclusions can be drawn from these two preliminary studies.

3.11 Anxiety with Associated Depression

This group includes patients diagnosed with predominantly anxiety symptoms but in whom significant depression was also present. It therefore differs from the mixed depressive-anxiety populations discussed in section 3.7 in whom neither symptom predominated. The group also includes studies which comprised mixed populations with a greater number of anxious than depressed patients in the population studied but which did not express results separately for each group. In these studies (table VI) it has generally been possible to show superiority of doxepin over chlordiazepoxide, diazepam and other anti-anxiety agents; presumably because of its antidepressant activity on the depressive symptoms of the patients in the populations studied. Thus, when anxiety is accompanied by depressive symptoms patients tend to respond better to doxepin than to chlordiazepoxide or diazepam. The effect of doxepin on anxiety usually occurs within the first week of treatment, with that on depression occurring later.

3.11.1 Comparison with Chlordiazepoxide in Anxiety with Depression

Gomez Martinez (1970) compared doxepin 75 to 150mg daily with chlordiazepoxide 30 to 60mg daily in 18 outpatients. Those patients in whom anxiety was not associated with depression appeared to respond well on both drugs, but when symptoms that could be interpreted as depressive were also present, doxepin proved much more effective (67% response) than chlordiazepoxide (37% response). Doxepin also had a greater effect on relief of insomnia. Although two other studies in outpatients could detect no difference between doxepin and chlordiazepoxide (Kingstone et al., 1970; Sim et al., 1971), other studies involving small numbers of patients have confirmed the trend for a more favourable response with

doxepin in patients with anxiety associated with depressive symptoms (Johnstone and Claghorn 1968; Simeon et al., 1970; Sterlin et al., 1972a). Thus, Simeon et al. (1970) found a significant advantage on clinical evaluation for doxepin 75 to 300mg daily over chlordiazepoxide 75 to 125mg daily during 8 weeks of treatment in 35 outpatients. Doxepin produced marked to moderate improvement in 10 of 12 patients who completed 8 weeks, compared with only 4 of 12 in the chlordiazepoxide group. Doxepin was also better tolerated in elderly patients, 3 of whom became ataxic on chlordiazepoxide.

In a comparative evaluation in 80 psychoneurotic outpatients, doxepin was shown to be superior in efficacy to chlordiazepoxide, hydroxyzine, meprobamate or phenobarbitone (Sterlin et al., 1972a). 40 patients received doxepin 75 to 225mg daily, but only 10 patients received each of the other drugs; chlordiazepoxide (30 to 90mg), hydroxyzine (75 to 225mg), meprobamate (600 to 1,800mg) or phenobarbitone (90 to 270mg). Only in the doxepin group were the total scores and individual items of the BPRS significantly different after 4 weeks from the baseline, and global evaluation showed a significantly greater proportion of improved patients in the doxepin group. Anxiety, guilt feelings, tension and depressive mood all improved with doxepin, which also produced the lowest incidence of side-effects. The groups were not matched in patient numbers and in addition, there was a greater proportion of depressed patients in the doxepin group.

3.11.2 Comparison with Diazepam in Anxiety with Depression

Three studies involving fairly large numbers of well-matched patient groups have indicated some advantage for doxepin over diazepam. Rickels et al. (1969) treated 69 hospital outpatients and general practice patients with fixed doses of 75mg doxepin or 6mg diazepam for 2 weeks, after which the doses were doubled. There was no significant overall difference between the groups, although the dose of diazepam was considered low by usually accepted standards in such patients. Doxepin produced more improvement than diazepam in depressive symptoms but not in symptoms of anxiety. Doxepin tended to produce more clinical improvement in general practice patients, while diazepam tended to produce more improvement in the outpatient clinic patients (fig. 6). At the dosages used, doxepin caused a greater incidence of drowsiness and autonomic side-effects, but all were mild and tended to decrease with time.

D'Elia et al. (1974) found that doxepin (55mg average daily) tended to have a more rapid onset of effect than diazepam (11mg daily) in 47 outpatients, and at 8 weeks doxepin had produced a significantly greater reduction in the total number of signs of anxiety and depression than diazepam. The degree of overall improvement in symptoms was similar for both drugs, but doxepin offered greater relief of depressive symptoms. Weight gain over 8 weeks was significantly more prevalent in the doxepin group. Bianchi and Phillips (1969) also found that doxepin (113mg daily) tended to produce a more favourable response than diazepam (21mg daily) in a group of 40 outpatients and 10 inpatients. Although there was no statistically significant difference between the drugs, doxepin tended to produce greater overall improvement as the 3 week study progressed (doxepin 56% markedly improved; diazepam 36%), and doxepin controlled depressive symptoms better. Side-effects of drowsiness, ataxia, constipation were more frequent with diazepam, and paraesthesia with doxepin.

3.11.3 Comparison with Trifluoperazine in Anxiety with Depression

In a double-blind cross over study in 20 patients, trifluoperazine (1.5 to 6mg daily) produced a greater improvement in symptoms of anxiety, and doxepin (30 to 150mg daily) a better response in depressive symptoms and sleep disturbance. Side-effects were much more troublesome with trifluoperazine (Kishore et al., 1973).

3.11.4 Anxiety/Depression Associated with Sleep Disturbances

Doxepin was significantly more effective than a placebo in anxious and depressed outpatients with

Table VI. Results of double-blind comparative trials in patients with predominantly anxiety associated with depression or with anxiety-depression syndrome

Author	Diagnosis	Population	Groups well matched[1]	Daily dosage doxepin (D)	Daily dosage other drug[2]	Duration	Efficacy[3] (see also text)	Onset of response	Side-effects (see also text)	Response rate (%)[4]			
										doxepin		other	
										+ +	+	+ +	+
Comparisons with chlordiazepoxide (C)													
Gomez-Martinez (1970)	Anxiety Anxiety with depression	Inpts (18)	...	75–100mg	30-60C	4w	D = C D > C (depressives)	—	D = C	50 ...	21 67 (depressives)	44 ...	33 37
Johnstone and Claghorn (1968)	Anxiety-depression (11) Psychoneurotic anxiety (9) Psychoneurotic depression (6) Other (4)	Outpts (30)	...	50–300mg	10–120mgC	6w	D > C	—	D > C	27	20	0	13
Kingstone et al. (1970)	Anxiety with depression	Outpts (30)	...	75–150mg	30–60mgC	3w	D = C	D = C	D = C	47	20	27	33
Sim et al. (1971)	Anxiety with depression	GP (65)	Yes	75–150mg	30–60mgC	6w	D = C	D = C	D > C	—		—	
Simeon et al. (1970)	Anxiety with depression (16) Depression (2) Other (3)	Outpts (21)	No (C)	100–300mg	75–125mgC	8–12w	D > C	D = C	D < C	42	42	11	33
Sterlin et al. (1972a)	Depressive neurosis (41) Anxiety neurosis (30) Phobic neurosis (4) Obsessive-compulsive neurosis (5)	Outpts (80)	No (D)	75–150mg	30–60mgC 75–150mgH 600–1,200mgM 90–180mgP	4w	D > C > H > M > P	—	D < P	...	...	...	...

Comparisons with diazepam (Di)													
Bianchi and Phillips (1972)	Anxiety neurosis with or without mild depression (37) Anxiety neurosis with moderately severe depression (13)	Outpts (40) Inpts (10)	Yes	100mg	20mgDi	3w	D = Di D > Di (depression)	D < Di	D < Di	56	28	36	32
d'Elia et al. (1974)	Anxiety with depression	Outpts (47)	Yes	60-80mg	12-16mgDi	8w	D = Di D > Di (depression)	D > Di	D > Di	—	—	—	—
Rickels et al. (1969)	Anxiety (26) Anxiety-depression (36) Depression (4) Other (3)	Outpts (39) GP (30)	—	75-150mg	6-12mgDi	4w	D > Di (depression) D > Di (GP) D < Di (outpts)	D > Di	D > Di	...	...	...	...
Comparison with amitriptyline (A) + chlordiazepoxide (C)													
Trappe (1975)	Severe anxiety, often with depression	Outpts (30)	—	75-300mg	75-300mgA 30-120mgC	4w	D > A-C	—	—	...	...	...	...

1 Population distribution favoured efficacy for drug indicated in parentheses, usually because of less patients with greater duration or severity of illness, and sometimes because of unequal distribution of patient types or previous treatment, etc. An elipsis (...) signifies insufficient information or not clear whether groups reasonably well matched. A dash (—) signifies no appropriate data provided. See also text.

2 Abbreviations: H = hydroxyzine; M = meprobamate; P = phenobarbitone.

3 Efficacy overall on basis of clinical (global) and psychiatric symptom rating scales. In many cases trends towards differences emerged between the study drugs. See text for explanation.

4 Response rate in terms of global clinical evaluation only. + + = remission or marked improvement; + = moderate improvement; (—) = no clinical assessment of results given; (...) = results not expressed as percentage. A figure only in + column signifies marked plus moderate improvement. See also text.

sleep disturbances (Goldberg and Finnerty, 1972a). Those in the doxepin group felt more rested upon awakening in the morning and found it easier to fall asleep at night. Relief of anxiety occurred within the first week and depression after this time. Other investigators have also commented on the improvement in sleep pattern by doxepin in anxious outpatients with associated depression and sleep disturbances (Ruiz Taviel, 1971).

4. Side-Effects

On the basis of the results of published and unpublished therapeutic trials doxepin is well tolerated; including in the elderly (see section 3.4) and patients with cardiovascular disease (see section 3.5). Although many patients experience side-effects, most are mild and generally disappear with continued treatment, or if necessary, by reduction of dosage (Ayd, 1969; Ciurezu and Timofte, 1974; Krakowski, 1968; Pitts, 1969; Rickels et al., 1969, 1972).

4.1 Comparisons With Other Drugs

The profile of side-effects reported (table VII) and to be expected is the same with doxepin as with other tricyclic antidepressants. However, in general, doxepin has caused fewer or less troublesome side-effects than imipramine or amitriptyline (tables I, II). The usual precautions for use of tricyclic antidepressants also apply to doxepin. In comparisons with chlordiazepoxide and diazepam in patients with anxiety and depression, the nature and incidence of side-effects have generally been similar (table VI), but in two studies doxepin caused a much smaller incidence of ataxia (Bianchi and Phillips, 1972; Simeon et al., 1970).

4.2 Common Side-Effects

Dry mouth, drowsiness or sedation, and constipation are the most common side-effects, but are often mild (table VIII). Excessive daytime drowsiness can generally be avoided by giving the major portion or the total daily dose at bedtime (e.g. Goldstein et al.,

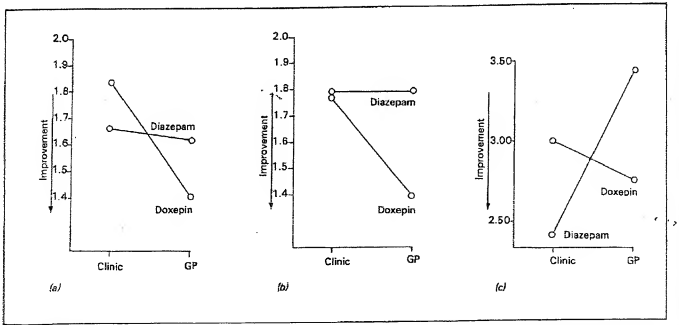


Fig. 6. Patients with anxiety associated with depression (after Rickels et al., 1969). (a) Response according to anxiety cluster of patient symptom checklist. (b) Response according to depression cluster of patient symptom checklist. (c) Response according to global (overall) estimate of psychopathology.

Table VII. Incidence of side-effects from studies analysed for this review and in analysis of Pitts (1969)

Side-effect	All patients (Pitt, 1969) N = 1706	All patients (this review) N = 1183[3]	Depressed patients[1] (this review) N = 917[3]	Anxious patients[2] (this review) N = 266
Drowsiness	17.4%	29.1%	28.5%	31.2%
Dry mouth	14.5%	27.0%	29.1%	19.5%
Constipation	4.4%	9.4%	10.3%	6.4%
Dizziness	5.9%	8.7%	7.5%	12.8%
Extrapyramidal reactions	6.3%	4.1%	3.6%	5.6%
Blurred vision	3.0%	3.8%	3.8%	3.8%
Sweating	2.7%	3.8%	3.2%	1.9%
Hypotension	2.8%	2.4%	3.0%	0
Tachycardia	2.6%	1.7%	1.6%	1.9%

1 Includes those with some anxiety component.
2 Includes those with some depression component.
3 1210 for drowsiness; 944 in depressed patients. Some studies recorded other side-effects but only gave data for drowsiness.

1973; Moser, 1969). The incidence of drowsiness does not seem to be related to the severity of the illness at the onset of treatment (Lang, 1970).

4.3 Less Common Side-Effects

Less commonly reported side-effects include extrapyramidal symptoms (usually mild and consisting of tremor, but sometimes akathisia or gait disturbance), blurred vision, postural hypotension, sweating and tachycardia. Urinary retention has been rare. Some investigators have reported instances of paresthesiae (Bianchi and Phillips, 1972; Bianchi et al., 1971; Haider, 1971), notable weight gain (d'Elia et al., 1974; Forsen, 1975), excitement (Goldstein et al., 1973; Sterlin et al., 1972a), and leukopenia and thrombocytopenia (Nixon, 1972). These and other infrequent side-effects are to be expected from tricyclic antidepressants. Liver function abnormalities have been noted by a number of investigators (Ayd, 1971, 1975b; Bauer and Nowak, 1969; Belsasso et al., 1969; Gallant et al., 1969; Nahunek et al., 1974; Poeldinger et al., 1966; Sim et al., 1971), but do not seem to be of any clinical significance.

Euphoria has been virtually absent and there have been no reports of physical dependence or withdrawal symptoms associated with doxepin therapy. Tricyclic antidepressants have not been associated with drug dependence problems.

4.4 Dosage and Incidence of Side-Effects

A few studies have examined the relationship of dosage to incidence of side-effects (fig. 7). In general, side-effects tended to be dose-related in a study involving males (Denber et al., 1975). Side-effects also tend to be dose-related in females (Rickels pers. comm., 1976). Drowsiness (Poeldinger et al., 1966) and tachycardia (Ayd, 1975b; Diehl, 1971) in particular appear to be dose related. Drowsiness occurred in 7% of patients at doses below 200mg and in 29% at doses above 200mg (Poeldinger et al., 1966). Headache also seems to be a function of dosage (Denber et al., 1975).

5. Overdosage

The pattern of tricyclic antidepressant overdosage is now well recognised (e.g. Bickel, 1975; Jefferson, 1975). Major complications include convulsions, respiratory depression, cardiac arrhythmias and dis-

Table VIII. Severity of side-effects (as percentage of each reaction) from studies analysed for this review and in analysis of Pitts (1969)

Side-effect	Pitts (1969)[1] N = 1706			This review N = 280		
	+	+ +	+ + +	+	+ +	+ + +
Drowsiness	41%	37%	19%	52%	26%	22%
Dry mouth	54%	32%	13%	69%	20%	11%
Constipation	41%	38%	21%	68%	17%	15%
Dizziness	39%	39%	16%	77%	13%	10%
Extrapyramidal reactions	55%	28%	17%	77%	23%	0%
Blurred vision	67%	21%	12%	92%	8%	0%
Sweating	41%	37%	17%	71%	29%	0%
Hypotension	61%	31%	8%	55%	36%	9%
Tachycardia	45%	42%	9%	80%	20%	0%

+ = mild; + + = moderate; + + + = marked

1 Severity not specified in some cases, and the % therefore does not total 100.

turbances of the EKG. Doxepin differs from the general pattern in possibly having less depressive effect on intracardiac conduction (Burrows et al., 1976a,b; Davies et al., 1975; see section 1.2.3), *but it may still cause lethal arrhythmias,* and by probably producing more marked respiratory depression (Williams, 1972).

5.1 Manifestations of Overdosage

Doxepin intoxication is characterised in mild cases by drowsiness, stupor, blurred vision, vertigo, agitation and excessive dryness of the mouth, leading in severe cases to coma, respiratory depression, hypotension, convulsions, cardiac arrhythmias and tachycardia. Other signs may include urinary retention and bladder atony, decreased gastrointestinal motility (paralytic ileus), hyperthermia or occasionally hypothermia, hypertension, mydriasis and hyperreflexia (Ducluzeau, 1973; Krakowski, 1968; Pebay-Peyroula et al., 1969; Radmayr, 1971; Williams, 1972).

The major signs of doxepin intoxication in adults usually appear after doses of at least 500mg (Ducluzeau, 1973). Patients have recovered, without complications other than transient coma, following ingestion of a combination of doxepin 3,750mg and diazepam 200mg (Pebay-Peyroula et al., 1969), or doxepin 2,500mg (27mg/kg) taken in association with a considerable amount of alcohol (Radmayr, 1971). The lowest lethal dose of doxepin alone in adults appears to have been about 1,300mg (Radmayr, 1971), which to the present compares with 950mg for amitriptyline and 625mg for imipramine (Bickel, 1975). There have been a number of fatal cases of doxepin poisoning (Norheim, 1973; Oliver and Watson, 1974; Radmayr, 1971).

Death has usually been associated with autopsy blood levels of the order of 1mg/100ml, with similar or slightly higher levels in the urine and brain, and markedly higher levels in the liver (Norheim, 1973;

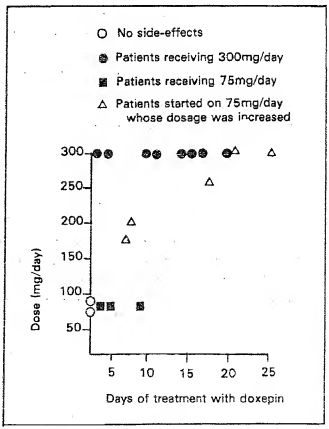


Fig. 7. First observation of side-effects in relationship to dosage. Symbols indicate number of patients in each group (after Denber et al., 1975).

Oliver and Watson, 1974). Blood levels of doxepin were 1.9mg/100ml and 1.1mg/100ml following fatal ingestion of about 2,500 and 1,500mg respectively (Oliver and Watson, 1974).

5.2 Suggested Treatment of Overdosage

Management consists of supportive treatment (Ducluzeau, 1973; Pfizer Laboratories Product Information, 1976). In mild cases, observation and supportive therapy is all that is usually necessary.

In severe cases, medical management consists of intensive supportive therapy. Because absorption may be less rapid than normally after severe poisoning, especially in view of the anticholinergic properties of doxepin, gastric lavage, with appropriate precautions to prevent pulmonary aspiration, is recommended for conscious and unconscious (after intubation) patients, even if relatively late after ingestion (Elonen and Mattila, pers comm. 1976). The use of activated charcoal has been recommended, as has continuous gastric lavage with saline for 24 hours or more. Because of enterohepatic circulation of tricyclic antidepressants, use of activated charcoal for longer periods may be useful (Jefferson, pers. comm. 1976). An adequate airway should be established in comatose patients, with assisted ventilation if necessary. EKG monitoring may be required for several days, since relapse after apparent recovery has been reported.

Arrhythmias should be treated with the appropriate antiarrhythmic agent. Because of the increased risk of conduction disturbances, quinidine and procainamide should not be used. Similarly, while large doses of a β-adrenoceptor blocking drug with 'quinidine-like' properties should not be used (e.g. propranolol), compounds without such membrane effects may be tried (e.g. practolol, metoprolol, atenolol, sotalol, timolol). If conduction block threatens, an intracardiac electrode for cardiac pacing should be inserted (Elonen and Mattila, pers comm. 1976). It has been reported that many of the cardiovascular and CNS symptoms of tricyclic antidepressant poisoning in adults may be reversed by the slow intravenous administration of 1 to 3mg of physostigmine salicylate. Because physostigmine is rapidly metabolized, the dosage should be repeated as required. Convulsions may respond to standard anticonvulsant therapy, but barbiturates may potentiate any respiratory depression. Dialysis and forced diuresis are generally not of value in the management of doxepin overdosage, because of the high tissue and protein binding properties of the drug.

6. *Drug Interactions*

6.1 Theoretically Possible Interactions

As with other tricyclic antidepressants, doxepin may enhance the sedative effects of various drugs such as hypnotics, antihistamines, tranquillisers, narcotics, and the anticholinergic effects of others such as gastrointestinal antispasmodics, antipsychotics, certain antihistamines (e.g. diphenhydramine, phenindamine, promethazine) and anticholinergic antiparkinsonian agents (Avery, 1976). Tolerance to alcohol may be lowered with risk of enhanced CNS depressant effects and possible impairment of psychomotor skills (see section 1.2.5).

Ayd (1973) has reviewed experience of combined use of doxepin with other drugs. 3,000 patients were involved in the survey and doxepin had been given regularly or intermittently with one or more drugs (usually 4) at the same time. Over 150 drugs had been used along with doxepin. These included psychotherapeutic drugs (e.g. antipsychotics, antianxiety agents and hypno-sedatives, antiparkinsonian agents, lithium, methylphenidate) and non-psychotherapeutic drugs (e.g. thyroid hormone, antihistamines, narcotic analgesics, antihypertensive drugs). All interactions that did occur were predictable on the basis of the pharmacologic properties of the drugs involved. No significant interactions other than those described above or involving guanethidine (see below) were noted.

Serious reactions (e.g. agitation, tremor, hyperpyrexia, coma) and even death have occurred after inadvertent concurrent use of tricyclic antidepressants

with monoamine oxidase inhibitors (MAOI). An interval of at least 2 weeks should be allowed after a MAOI has been discontinued and cautious treatment with doxepin commenced. The exact length of time between withdrawal of a MAOI and commencement of a tricyclic antidepressant depends on the particular MAOI involved, the length of time it has been given, and the dosage employed. Planned use of doxepin and a MAOI has been successfully and safely employed in patients who have not responded to maximally tolerated doses of a tricyclic antidepressant (Ayd, 1973).

6.2 Interaction with Guanethidine and Related Adrenergic Neuron Blocking Agents

Doxepin only has a moderate inhibitory effect on the norepinephrine pump (see section 1.2.2); the same uptake mechanism by which the antihypertensive drugs guanethidine, bethanidine and debrisoquine enter the adrenergic neuron. Thus, at doses up to 150mg daily, doxepin does not antagonise the antihypertensive effects of concomitantly administered guanethidine or bethanidine, although doses of 200mg or more daily progressively produce blockade (Fann et al., 1971; Oates et al., 1969).

These investigators studied the effects of doxepin on blood pressure control by guanethidine or bethanidine in 3 hypertensive patients. Whereas desipramine 50mg daily produces a total and rapid antagonism of the antihypertensive effects of bethanidine (Oates et al., 1969), antagonism by doxepin in the 1 patient studied was less marked and developed only slowly (over 2 to 4 days); even at a dose of 300mg daily (Fann et al., 1971). At 200 to 300mg daily, doxepin also produced a significant antagonism of the antihypertensive effects of guanethidine (80mg daily in 1 patient, 50 and then 200mg daily in the other), though again this was less marked than that which is seen with desipramine. During the first 3 days after cessation of doxepin, blood pressure increases even further then takes 6 to 12 or more days to return to pre-doxepin levels (fig. 8).

In another investigation (Gerson et al., 1970), 9 elderly hypertensive subjects stabilised on guanethidine (50 to 150mg daily) or methyldopa (dose not stated) were given gradually increasing doses of doxepin (to 100mg daily in 9 patients; 200mg 4 patients; 250mg 2 patients) over a period of up to 8.5 weeks. No alteration of blood pressure control was noted, but the number of patients taking guanethidine was not stated. It is uncertain whether tricyclic antidepressants have any effect on blood pressure control with methyldopa (Avery, 1976; Jefferson, 1975; Simpson, 1976).

Clinical experience has confirmed the experimental findings of Fann and his group. Thus Ayd (1975b) did not find any antagonism of guanethidine in 2 patients who received doxepin 200mg daily but did observe some antagonism at doses of 300mg daily in another patient (Ayd, 1971). Experience of other clinicians indicates that doxepin does not antagonize the antihypertensive effect of guanethidine until doses of 200mg daily are reached. Higher doses progressively inhibit the action of guanethidine. At doses of 300mg or more daily, doxepin will usually completely reverse the antihypertensive effect of guanethidine (Ayd, 1973).

A few outpatients and some hospitalised patients with depression require doses of 200 to 300mg or more daily for an effective response (see section 7). Whether depression associated with hypertension will follow the same general pattern is not clear. Obviously, before doxepin is considered in any depressed hypertensive patient, it is essential to make sure that the antihypertensive drugs (e.g. Rauwolfia drugs, methyldopa, clonidine, propranolol) are not causing or aggravating the depression. Many clinicians now prefer to use a β-adrenoceptor blocking drug in hypertensive patients who require a tricyclic antidepressant (Simpson, 1976). Doxepin and other tricyclic antidepressants do not appear to interfere with blood pressure control by β-adrenoceptor blocking drugs (Avery, 1976). Doxepin itself causes a very low incidence of postural hypotension and has not affected blood pressure control in treated hypertensive patients (see section 3.5).

7. Dosage

Dosage should be individualised. Unfortunately, many studies have used fixed dosage schedules or have imposed an arbitrary upper limit to dosage.

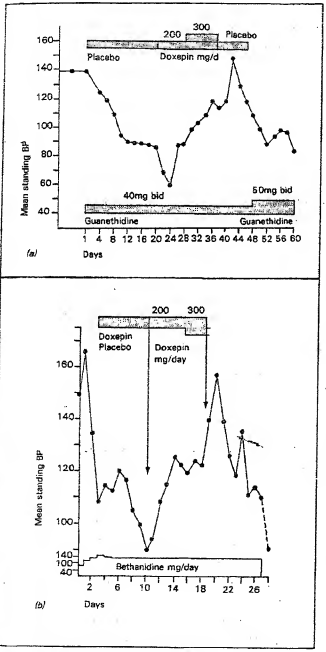


Fig. 8. Antagonism of antihypertensive effect of (a) guanethidine and (b) bethanidine by doxepin. Note the increased antagonistic effect which occurs during the first 3 days after withdrawal of doxepin (after Fann et al., 1971).

However, a general pattern does emerge from the published and unpublished literature* (see section 3).

In depression in outpatients, 75 to 150mg daily has been the generally used dosage, with a few patients requiring 200 to 300mg or more (e.g. Ayd, 1969; Krakowski, 1968). Hospitalised patients and those with more severe illness have generally been treated with 150 to 300mg daily, with a few patients requiring and tolerating up to 500mg (e.g. Castrogiovanni et al., 1971; Krakowski, 1968; Poeldinger et al., 1966). Patients with psychotic depression generally require larger doses than those with neurotic depression (e.g. Gillmer, 1970). Dosage in the elderly has involved smaller doses initially, with smaller progressive increases, generally up to 150mg daily, but some elderly patients have needed and tolerated larger doses (see section 3.4). Preliminary studies suggest that there is a correlation between plasma levels and response (see section 2.2.2).

Patients with anxiety or anxiety associated with depressive symptoms have generally required lower doses than those used in depression and have usually been in the range of 75 to 150mg daily for outpatients. Hospitalised patients and some patients with anxiety associated with depression may require up to 300mg daily (e.g. Simeon et al., 1970; Sterlin et al., 1970, 1971, 1972a).

A number of investigators have successfully given the major portion of the daily dosage, or the total daily dosage, at bedtime. The daily amounts have ranged up to 300mg (e.g. Ayd, 1973; Friedel and Raskind, 1975; Goldberg et al., 1974).

A bedtime-based dosage regimen is particularly suitable in the elderly (see section 3.4) and when it is necessary to overcome or minimise any excessive daytime drowsiness (see section 4.2). A single daily dose at bedtime is especially beneficial in depressed patients with sleep disturbances (see section 3.3).

* Some of the doses mentioned in this section exceed the recommended maximum in the USA, where clinicians have to consult the manufacturers product information for guidance. The maximum recommended daily dose in the USA is 300mg and for single daily dose regimens 150mg.

Increases in dosage of tricyclic antidepressants should always be gradual, particularly in the elderly and when increasing dosage in bedtime-based dose schedules.

References

Aceto, M.D.: The antinicotinic effects of drugs with clinically useful sedative-antianxiety properties. Pharmacology 13: 458 (1975).

Avery, G.S.: Guide to clinically significant drug interactions, p.936, 938. Drug Treatment: Principles and Practice of Clinical Pharmacology and Therapeutics (ADIS Press, Sydney; Publishing Sciences Group, Boston; Churchill Livingstone, Edinburgh 1976).

Alix, B.: Etude en double aveugle de la doxepin et d'un anxiolytique d'utilisation courante en therapeutique cardiologique. Medicine et Hygiene 27: 1425 (1969).

Ayd, F.J.: A clinical evaluation of doxepin (Sinequan). Diseases of the Nervous System 30: 396 (1969).

Ayd, F.J.: Long-term administration of doxepin (Sinequan). Diseases of the Nervous System 32: 617 (1971).

Ayd, F.J.: Doxepin with other drugs. Southern Medical Journal 66: 465 (1973).

Ayd, F.J.: Single daily dose of antidepressants. Journal of the American Medical Association 230: 263 (1974).

Ayd, F.J.: Central anticholinergic activity and tricyclic antidepressant efficacy. International Drug Therapy Newsletter 10: 21 (1975a).

Ayd, F.J.: Maintenance doxepin (Sinequan) therapy for depressive illness. Diseases of the Nervous System 36: 109 (1975b).

Bacal, B.; Amarilho do, I.P.; Zamijevski, M. and Lion, M.F.: Doxepin action on neurotic patients with cardiac symptomatology. Hospital 76: 1733 (1969).

Ban, T.A.: A comparative clinical and conditioning study with doxepin and diazepam in psychoneurotic patients. Personal communication (1976).

Barth, N.; Manns, M. and Muscholl, E.: Arrhythmias and inhibition of noradrenaline uptake caused by tricyclic antidepressants and chlorpromazine on the isolated perfused rabbit heart. Naunyn-Schmiedeberg's Archives of Pharmacology 288: 215 (1975).

Barth, N. and Muscholl, E.: The effects of the tricyclic antidepressants desipramine, doxepin and iprindole on the isolated perfused rabbit heart. Naunyn-Schmiedeberg's Archives of Pharmacology 284: 215 (1974).

Bauer, G. and Nowak, H.: Doxepin, a new antidepressant: Comparison of activity with amitriptyline. Arzneimittel-Forschung 19: 1642 (1969).

Beaubien, J.; Ban, T.A.; Lehmann, H.E. and Jarrold, L.: Doxepin in the treatment of psychoneurotic patients. Current Therapeutic Research 12: 192 (1970).

Beber, C. and Georgia, E.H.: Before ECT — A psychopharmacological approach to the treatment of the clinically depressed geriatric patient. Presented at the American Geriatrics Society Annual Meeting April 16-17 (Miami, Florida 1975).

Belsasso, G.; Lara Tapia, H. and Grajales, A.: Clinical investigation with doxepin, a new antidepressant. Current Therapeutic Research 11: 165 (1969).

Bergener, M. and Behrends, K.: Zur klinischen Prufung von Doxepin, einer neuartigen antidepressiv wirksamen substanz. Arzneimittel-Forschung 16: 1617 (1966).

Bianchi, G.N.; Barr, R.F. and Kiloh, L.G.: A comparative trial of doxepin and amitriptyline in depressive illness. Medical Journal of Australia 1: 843 (1971).

Bianchi, G.N. and Phillips, J.: A comparative trial of doxepin and diazepam in anxiety states. Psychopharmacologia 25: 86 (1972).

Bickel, M.H.: Poisoning by tricyclic antidepressant drugs. General and pharmacokinetic considerations. International Journal of Clinical Pharmacology 11: 145 (1975).

Blaine, G.: Double-blind comparison of doxepin and amitriptyline in depressed menopausal outpatients receiving estrogen replacement therapy; in Mendels (Ed.) Sinequan: A monograph of recent studies, p.43 (Excerpta Medica, Amsterdam 1975).

Bohlau, V.; Schildwuchter, G. and Bohlau, E.: Doxepin in der praklinischen geriatrie. Medizinische Monatsschrift 26: 422 (1972).

Boysen, K.H.; Hackl, H. and Lackner, M.: Double-blind trial with doxepin and opipramol in patients with vegetative depressive symptoms. Praxis 59: 1242 (1970).

Brogden, R.N.; Speight, T.M. and Avery, G.S.: Doxepin. A review. Drugs 1: 194 (1971).

Buczko, W.; De Gaetano, G. and Garattini, S.: Influence of some tricyclic antidepressive drugs on the uptake of 5-hydroxytryptamine by rat blood platelets. Journal of Pharmacy and Pharmacology 26: 814 (1974).

Bukowczyk, A. et al.: Study of the antidepressant activity of doxepin (Sinequan). Preliminary report. Psychiatria Polska 2: 197 (1971).

Burrows, G.D.; Mowbray, R.M. and Davies, B.: A sequential comparison of doxepin (Sinequan) and placebo in depressed patients. Medical Journal of Australia 1: 364 (1972).

Burrows, G.D.; Vohra, J.; Hunt, D.; Sloman, J.G.; Scoggins, B.A. and Davies, B.M.: The effects on the heart of different tricyclic antidepressants. Presented at the Royal College of Psychiatrists, London, July (1975).

Burrows, G.D.; Vohra, J.; Hunt, D.; Sloman, J.G.; Scoggins, B.A. and Davies, B.: Cardiac effects of different tricyclic antidepressant drugs. British Journal of Psychiatry 129: 335 (1976a).

Burrows, G.D.; Vohra, J.; Dumovic, P., Maguire, K.; Scoggins, B.A. and Davies, B.: Tricyclic antidepressant drugs and cardiac conduction. Progress in Neuro-Psychopharmacology. In press (1976b).

Butterworth, A.T. and Watts, R.D.: Treatment of hospitalised alcoholics with doxepin and diazepam. A controlled study. Quarterly Journal of Studies on Alcohol 32: 78 (1971)

Castrogiovanni, P.; Placidi, G.F.; Maggini, C.; Ghetti, B. and Cassano, G.B.: Clinical investigation of doxepin in depressed patients. Pilot open study, controlled double-blind trial versus imipramine, and all-night polygraphic study. Pharmakopsychiatrie Neuro-Psychopharmakologie 4: 170 (1971).

Chaplan, A.: Doxepin in anxious/depressed outpatients with gastrointestinal symptoms: Double-blind comparison of doxepin and perphenazine/amitriptyline; in Mendels (Ed.) Sinequan: A monograph of recent clinical studies, p.32 (Excerpta Medica, Amsterdam 1975).

Charatan, F.B.: Depression in old age. New York State Journal of Medicine 75: 2505 (1975).

Chaudhry, M.R.; Ishaq, M. and Suleman, M.: Double blind study with sinequan (doxepin) vs diazepam vs placebo in psychoneurosis. Journal of the Pakistan Medical Association 20: 315 (1970).

Chien, C.P.; Stotsky, B.A. and Cole, J.O.: Psychiatric treatment for nursing home patients — drug, alcohol and milieu. American Journal of Psychiatry 130: 543 (1973).

Ciurezu, T. and Timofte, G.: Doxepin therapy in outpatients with depressive anxious states. Revue Roumaine Medicale 12: 143 (1974).

Clark, C.J. and Downie, C.C.: A method for the rapid determination of the number of patients to include in a controlled clinical trial. Lancet 2: 1357 (1966).

Coleman, J.: Severe emotional disturbance associated with physical illness. I. Double-blind study. Psychosomatics 10 (Section II): 32 (1969).

Constantine, J.W.; Scriabine, A.; Smith, S.G.; McShane, W.K. and Booker, Katherine D.: Antispasmodic and vasodilator activities of doxepin. Journal of New Drugs 4: 249 (1964).

Coppen, A.; Gupta, R.; Montgomery, S.; Ghose, K.; Bailey, J.; Burns, B. and De Ridder, J.J.: Mianserin hydrochloride: A novel antidepressant. British Journal of Psychiatry 129: 342 (1976).

Davies, B.; Burrows, G.D.; Dumovic, P.; Vohra, J.; Hunt, D.; Sloman, G. and Scoggins, B.: Effects on the heart of different tricyclic antidepressants; in Mendels (Ed) Sinequan: A monograph of recent clinical studies, p.54 (Excerpta Medica, Amsterdam 1975).

d'Elia, G.; von Knorring, L.; Marcusson, J.; Mattsson, B.; Perris, C. and Persson, G.: A double-blind comparison between doxepin and diazepam in the treatment of states of anxiety. Acta Psychiatrica Scandinavica Suppl. 255: 35 (1974).

Denber, H.C.; Boone, W.F. and Tuchman, M.M.: High versus low dose doxepin in depressed patients: A controlled study, in Mendels (Ed) Sinequan: A monograph of recent clinical studies, p.59 (Excerpta Medica, Amsterdam 1975).

Diehl, L.W.: On the treatment of depressive syndrome with doxepin in the hospital. Medizinische Welt 45: 1805 (1971).

Downing, R.W. and Rickels, K.: Mixed Anxiety-depression. Archives of General Psychiatry 30: 312 (1974).

DuBois, R.: A trial of doxepin in the treatment of the anxiety-depression-somatization complex in internal medicine: A study of 32 cases. Medicine et Hygiehe 27: 1428 (1969).

Duchuzeau, R.: Les intoxications a la doxepine. Bulletin de Medicine Legale et de Toxicologie Medicale 16: 281 (1973).

Duffiey, R.G.: Use of psychotherapeutic drugs in the acute detoxification of heroin addicts. Military Medicine 138: 748 (1973).

Dunleavy, D.L.F.; Brezinova, V.; Oswald, I.; MacLean, A.W. and Tinker, M.: Changes during weeks in effects of tricyclic drugs on the human sleeping brain. British Journal of Psychiatry 120: 663 (1972).

Ebie, J.C.: Doxepin and a combination of amitriptyline and chlordiazepoxide in the treatment of anxiety-depression syndrome — A double-blind trial. Ghana Medical Journal 13: 33 (1974).

Elonen, E.: Correlation of the cardiotoxicity of tricyclic antidepressants to their membrane effects. Medical Biology 52: 415-423 (1974).

Elonen, E.: Effect of β-adrenoreceptor blocking drugs, physostigmine, and atropine on the toxicity of doxepin in mice. Medical Biology 53: 231 (1975).

Elonen, E., Linnoila, M.; Lukkari, I. and Mattila, M.J.: Concentration of tricyclic antidepressants in plasma, heart and skeletal muscle after their intravenous infusion to anaesthetized rabbits. Acta Pharmacologica et Toxicologica 37: 274 (1975).

Elonen, E.; Mattila, M.J. and Saarnivaara, L.: Cardiovascular effects of amitriptyline, nortriptyline, protriptyline and doxepin in conscious rabbits. European Journal of Pharmacology 28: 178 (1974).

Elonen, E. and Mattila, M.J.: Cardiovascular effects of amitriptyline, nortriptyline, protriptyline and doxepin in conscious rabbits after sub-acute pretreatment with protriptyline. Medical Biology 53: 238 (1975).

Elwan, O.; Taher, Y.; Allam, M. and Hassan, M.A.: A comparative study of antidepressants in the treatment of depressive states. Journal of International Medical Research 4: 202 (1976).

Evans, W.; Gensler, F.; Blackwell, B. and Galbrecht, C.: The effects of antidepressant drugs on pain relief and mood in the chronically ill. A double-blind study. Psychosomatics 14: 214 (1973).

Fann, W.E.; Cavanaugh, J.H.; Kaufmann, J.S.; Griffith, J.D.; Davis, J.M.; Janowsky, D.S. and Oates, J.A.: Doxepin: Effects on transport of biogenic amines in man. Psychopharmacologia 22: 111 (1971).

Fann, W.E.; Davis, J.M.; Janowsky, D.S.; Kaufmann, J.S.; Cavanaugh, J.H. and Oates, J.A.: Effect of antidepressant and

antimanic drugs on amine uptake in man. Journal of Nervous and Mental Disease 158: 361 (1974).

Fielding, J.M.; Mowbray, R.M. and Davies, B.: Trial of an anti-anxiety compound — doxepin ('Sinequan'). Psychopharmacologia 15: 134 (1969a).

Fielding, J.M.; Mowbray, R.M. and Davies, B.: A preliminary controlled study of doxepin ('Sinequan') as an antianxiety drug. Medical Journal of Australia 2: 851 (1969b).

Forsen, A.: Doxepin in the treatment of climacteric symptoms. A double-blind pilot study. Current Medical Research and Opinion 2(Suppl.): 51 (1975).

Friedel, R.O. and Raskind, M.A.: Relationship of blood levels of Sinequan to clinical effects in treatment of depression in aged patients; in Mendels (Ed) Sinequan: A monograph of recent clinical studies, p.51 (Excerpta Medica, Amsterdam 1975).

Gabay, S.; King, P. and Achee, F.M.: Characteristics of MAO activity in purified brain mitochondria with reference to the question of multiple forms. Presented at the 5th International Meeting of the International Society for Neurochemistry, Barcelona, Spain (1975).

Gallant, D.M.; Bishop, M.P.; Guerrero-Figueroa, R.; Selby, M. and Phillips, R.: Doxepin versus diazepam: A controlled evaluation in 100 chronic alcoholic patients. Journal of Clinical Pharmacology 9: 57 (1969).

Garcia-Torres, F.: Preliminary experience with doxepin (P-3693-A), in the treatment of depression. Actualidad Medica 517: 23 (1968).

General Practitioner Research Group: A comparison between dothiepin and doxepin in the treatment of depression. Practitioner 216: 581 (1976).

Gerson, I.M.; Friedman, R. and Unterberger, H.: Non-antagonism of antiadrenergic agents by a dibenzoxepine (Preliminary Report). Diseases of the Nervous System 31: 780 (1970).

Gillmer, R.E.: Treatment of the depressive reaction: A clinical evaluation of a new psychotherapeutic drug, doxepin (Sinequan). South African Medical Journal 44: 1386 (1970).

Glick, B.S.: Comparison of doxepin and thioridazine in outpatients. Diseases of the Nervous System 34: 37 (1973).

Glowinski, J. and Axelrod, J.: Effect of drugs on the uptake, release and metabolism of H^3-norepinephrine in the rat brain. Journal of Pharmacology and Experimental Therapeutics 149: 43 (1965).

Goldberg, H.L. and Finnerty, R.J.: The use of doxepin in the treatment of symptoms of anxiety neurosis and accompanying depression: A collaborative controlled study. American Journal of Psychiatry 129: 74 (1972a).

Goldberg, H.L. and Finnerty, R.J.: Depression/anxiety sleep. Presented at the Annual Meeting of the Massachusetts Medical Society, Boston, Massachusetts, May (1972b).

Goldberg, H.L. and Finnerty, R.J.: Evaluation of h.s. versus t.i.d. dosage in the treatment of clinical depression/anxiety with accompanying sleep disturbances. Presented at Glover Memorial Hospital, Massachusetts, April (1973).

Goldberg, H.L.; Finnerty, R.J. and Cole, J.O.: Doxepin: Is a single daily dose enough? Amer. J. Psych. 131: 1027 (1974a).

Goldberg, H.L.; Finnerty, R.J.; Nathan, L. and Cole, J.O.: Doxepin in single bedtime dose in psychoneurotic outpatients. Archives of General Psychiatry 31: 513 (1974b).

Goldberg, H.L.; Finnerty, R.J. and Cole, J.O.: The effect of doxepin in the aged: Interim report on memory changes and EKG findings; in Mendels (Ed) Sinequan: A monograph of recent clinical studies, p.65 (Excerpta Medica, Amsterdam 1975a).

Goldberg, H.; Finnerty, R.; Cole, J. and Rickels, K.: Collaborative studies in private practice. Comparison of doxepin and imipramine. Presented at the American College of Neuropsychopharmacology Meeting, Puerto Rico, Dec. 1975 (1975b). [Also reported by Goldberg, Finnerty and Rickels, unpublished data, Pfizer Laboratories 1976].

Goldstein, B.J. and Pinosky, D.G.: Clinical evaluation of doxepin in anxious depressed outpatients. Current Therapeutic Research 11: 169 (1969).

Goldstein, B.J.; Brauzer, B.; Steinbook, R.M. and Jacobson, A.F.: Psychotropic drug treatment of mixed anxiety and depression in non-psychiatric office patients: Expected and unexpected findings comparing doxepin, chlordiazepoxide and placebo. Southern Medical Journal 66: 892 (1973).

Gomez-Martinez, I.: Preliminary double-blind clinical trial with a new antidepressive, doxepin. Current Therapeutic Research 10: 116 (1968).

Gomez-Martinez, I.: Preliminary double-blind comparative study with doxepin and chlordiazepoxide in the treatment of anxiety. Munchener Medizinische Wochenschrift (Spanish Edition) 4: 391 (1970).

Gomide, C.H.A.: Clinical experience with doxepin. A double-blind study: Doxepin vs placebo. Folha Med 59: 553 (1969).

Gonzalez, J.V.: Comparative experience in the use of doxepin. Revue Medico Cirugia 33(6): 246-250 (1967).

Grof, R.; Saxena, B.; Cantor, R.; Daigle, L.; Hetherington, D. and Haines, T.: Doxepin versus amitriptyline in depression. A sequential double-blind study. Current Therapeutic Research 16: 470 (1974).

Guzman-Vilar, T.: Comparative experience with doxepin, chlordiazepoxide and placebo in neurovegetative problems. Revista Medicina y Cirugia (Colombia) 33: 105 (1969).

Hackett, Elizabeth; Gold, R.L.; Kline, N.S. and Winick, L.: Controlled evaluation of psychotropic drugs in a private psychiatric practice. Psychosomatics 8: 162 (1967).

Hackett, Elizabeth and Kline, N.S.: Antidepressant activity of doxepin and amitriptyline. A double-blind evaluation. Psychosomatics 10 (Section II): 21 (1969).

Haider, I.: A comparative trial of doxepin and amitriptyline in cases of depressive illness. Journal of the Pakistan Medical Association 21: 353 (1971).

Hano, J.; Sowinska, H. and Baran, L.: Central action of doxepin. Dissertationes Pharmaceutica et Pharmacologica 24: 415 (1972).

Hart, F.D.: Rheumatic disorders; in Avery (Ed) Drug Treatment, p.624 (ADIS Press, Sydney; Publishing Sciences Group, Acton; Churchill Livingstone, Edinburgh 1976).

Hasan, K.Z. and Akhtar, M.I.: Double-blind clinical study comparing doxepin and imipramine in depression. Current Therapeutic Research 13: 327 (1971).

Haslam, M.T.: A comparative trial of lorazepam and doxepin in the treatment of anxiety. Current Medical Research and Opinion 2: 240 (1974).

Hecht, Y.: A double-blind trial of doxepin and a commonly used anxiolytic in patients in a gastroenterologic survey. Medicine et Hygiene 27: 1427 (1969).

Hobbs, D.C.: Distribution and metabolism of doxepin. Biochemical Pharmacology 18: 1941 (1969).

Hollanda, L.; da Silva, C.N.A.; Lira, B.S., and Ferreira, S.C.: A double-blind clinical study with a new psychotropic doxepin vs placebo. O Hopital 77: 59 (1970).

Hollister, L.E.: Doxepin hydrochloride (Drugs five years later). Annals of Internal Medicine 81: 360 (1974).

Israel, L.; Michel, D.; Weil, J. and Wysoki, V.: Doxepin and librium. Annales Medico-Psychologiques 3: 465-469 (1970).

Jefferson, J.W.: A review of the cardiovascular effects and toxicity of tricyclic antidepressants. Psychosomatic Medicine 37: 160 (1975).

Johnstone, E.E. and Claghorn, J.L.: Doxepin versus chlordiazepoxide. A controlled comparison in neurotic outpatients. Current Therapeutic Research 10: 514 (1968).

Jones, B.L.; Eastgate, N.O.; Downey, P.G. and Davies, L.J.H.: A comparison of doxepin with diazepam and amitriptyline in general practice. New Zealand Medical Journal 76: 174 (1972).

Joost, H.G.; Poser, W. and Panten, U.: Inhibition of insulin release from the rat pancreas by cyproheptadine and tricyclic antidepressants. Naunyn-Schmiedeberg's Archives of Pharmacology 285: 99 (1974).

Kales, A.; Dement, W.G.; Tan, T.L.; Zarcone, V.; Hoddes, E.; Carshadan, M. and Kales, J.D.: Effects of Sinequan on sleep of insomniac subjects. Psychophysiology 9: 93 (1972).

Kaneto, H.; Koida, M. and Tsuchie, F.: Studies on tolerance and physical dependence producing liability of doxepin. Folia Pharmacologica Japonica 68: 704 (1972).

Karacan, I.; Blackburn, A.B.; Thornby, J.I.; Okawa, M.; Salis, P. J. and Williams, R.L.: The effect of doxepin HCl (Sinequan) on sleep patterns and clinical symptomatology of neurotic depressed patients with sleep disturbance; in Mendels (Ed) Sinequan: A monograph of recent clinical studies. p.4 (Excerpta Medica, Amsterdam 1975).

Karacan, I. and Williams, R.L.: Advances in the pharmacology of sleep. Presented as a scientific exhibit at the 129th Annual Meeting of the American Psychiatric Association, Miami Beach, May (1976).

Karacan, I.; Williams, R.L. and Salis, P.J.: Sleep and sleep abnormalities in depression; in Fann, Karacan, Pokorny and Williams (Eds) Phenomenology and Treatment of Depression, p.167 (Spectrum, New York 1977).

Karobath, M.E.: Tricyclic antidepressive drugs and dopamine-sensitive adenylate cyclase from rat brain striatum. European Journal of Pharmacology 30: 159 (1975).

Kasich, A.M.: A controlled trial of doxepin and diazepam in the treatment of anxiety accompanying gastrointestinal disease. British Journal of Clinical Practice 23: 121 (1969a).

Kasich, A.M.: Clinical evaluation of doxepin and diazepam in patients with gastrointestinal disease and anxiety. A controlled double-blind study and long-term evaluation. Psychosomatics 10 (Section II): 18 (1969b).

Kiev, A.: The role of chemotherapy in managing potentially suicidal patients. Diseases of the Nervous System 35: 108 (1974).

Kimura, M.; Nakagawa, T.; Suehiro, K.; Kono, T.; Takayama, T. and Nagato, H.: A double-blind comparison of clinical efficacy of doxepin and imipramine in depressive patients. Presentation at International Congress of Psychosomatic Disease, Italy, August (1975).

Kimura, Y.; Kume, M. and Kageyama, K.: Absorption, distribution and metabolism of doxepin hydrochloride. Pharmacometrics 6: 955 (1972).

Kingstone, E.; Kolivakis, T. and Kossatz, I.: Doxepin versus chlordiazepoxide: A double-blind study on anxious outpatients. Current Therapeutic Research 12: 213 (1970).

Kishore, B.; Kaur, A. and Verma, R.S.: A comparative study of doxepin versus trifluoperazine in anxiety neurosis. Journal of the Indian Medical Association 60: 280 (1973).

Kline, N.S.; Cooper, T. and Johnston, B.: Doxepin and desmethyldoxepin serum levels and clinical response; in Gottschalk and Merlis (Eds) Pharmacokinetics of Psychoactive Drugs: Blood Levels and Clinical Response, p.221 (Spectrum, New York 1976).

Knott, D.H.; Beard, J.D. and Fink, R.D.: Alcoholism. The physician's role in diagnosis and treatment. Presented as a scientific exhibit at the 125th Annual Meeting of the American Psychiatric Association, Dallas, May (1972).

Koe, B.K. and Constantine, J.W.: Blocking H^3-norepinephrine uptake and some guanethidine-induced effects with tricyclic antidepressant drugs. Archives Internationales Pharmacodynamie et de Therapie 195: 71 (1972).

Koknel, O. and Eper, O.: A study with Sinequan (Doxepin) Diseases of the Nervous System 32: 405 (1971).

Krakowski, A.J.: Activity study of doxepin, a new antidepressant. Psychosomatics 9: 89 (1968).

Krakowski, A.J.: Biphasic drugs in the treatment of depression with anxiety. Psychosomatics 10 (Section II): 7 (1969).

Krasner, E.B.: Double-blind comparative trial of doxepin and chlordiazepoxide in general practice. British Journal of Clinical Practice 25: 555 (1971).

Kulkarni, A.S. and Bocknik, S.E.: Interaction of Ro 4-1284 with doxepin, amitriptyline and desmethylimipramine on mouse avoidance behaviour. Europ. J. Pharmacol. 22: 59 (1973).

Laffranchini, S.: A double-blind comparative trial of Sinequan and Limbitrol. Medecine et Hygiene 29: 227 (1971).

Lang, W.R.: Trial of a new psychotropic drug, doxepin. New Zealand Medical Journal 72: 181 (1970).

Lassen, J.B.: The effect of p-chloroamphetamine on motility in rats after inhibition of monoamine synthesis, storage, uptake and receptor interaction. Psychopharmacologia 34: 243 (1974).

Lee, R.E.: The influence of psychotropic drugs on prostaglandin biosynthesis. Prostaglandins 5: 63 (1973).

Lingjaerde, O.: Effect of doxepin on uptake and efflux of serotonin in human blood platelets in vitro. Psychopharmacology 47: 183 (1976).

Majczak, A.; Masiak, M.; Grzywa, Anna; Gorniewicz, Anna and Komada, Joanna: Zastrosowanie sinequanu w leczeniu roznych form klinicznych depresji. Psychiatria Polska 9: 51 (1975).

Marble, A., Selenkow, H.A.; Rose, L.I.; Dluhy, R.G. and Williams, G.H.: Endocrine diseases; in Avery (Ed) Drug Treatment, p.422 (ADIS Press, Sydney; Publishing Sciences Group, Boston; Churchill Livingstone, Edinburgh 1976).

McLaughlin, B.: Management of psychoneurotic anxiety and depression in outpatients. Psychosomatics 10 (Section II): 28 (1969).

Mendels, J. and Hawkins, D.R.: Sleep and depression. Further considerations. Archives of General Psychiatry 19: 445 (1968).

Mendels, J. and Schless, A.: A controlled comparison of doxepin h.s. and doxepin q.i.d. Journal of Clinical Pharmacology 15: 534 (1975).

Miletto, G.: La doxepine en pratique psychiatrique. Doses fortes — cures prolongees. Psychologie Medicale 4: 805 (1972).

Milner, G. and Landauer, A.A.: The effects of doxepin, alone and together with alcohol, in relation to driving safety. Medical Journal of Australia 1: 837 (1973).

Mises, R. and Moniot, M.: Double-blind comparative study of doxepin and medazepam in adolescents. Annales Medico-Psychologiques 129: 431 (1971).

Mivelaz, M.: Doxepin in psychiatric out-patients. Medecine et Hygiene 27: 1425 (1969).

Molinengo, L. and Ricci-Gamalero, S.: The action of imipramine, amitriptyline, doxepin and butriptyline in an operant conditioning schedule. Psychopharmacologica 24: 247 (1972).

Montgomery, B.A.; Cullinan, T.R. and Bayley, A.J.: A double-blind comparative trial of doxepin hydrochloride and chlordiazepoxide in anxiety and depression in general practice. British Journal of Clinical Practice 24: 207 (1970).

Moore, R.H. and White, R.P.: Central anticholinergic actions of doxepin in rabbits. Archives Internationales Pharmacodynamie et de Therapie 213: 113 (1975).

Moser, A.: Doxepin in geriatrics. Medecine et Hygiene 27: 1425 (1969).

Mundo, A.S.; Bonaccorsi, A.; Bareggi, S.R.; Franco, R.; Morselli, P.L.; Riva, E. and Garattini, S.: Relationships between tricyclic antidepressant concentrations, ^{3}H-noradrenaline uptake and chronotropic effect in isolated rat atria. European Journal of Pharmacology 28: 368 (1974).

Muratorio, A.; Maggnini, C. and Murri, L.: Effects of P-3693-A on night sleep of depressed subjects. Neuropsichiatria 33: 179 (1967).

Naftulin, D.H. and Ware, J.E.: A behavioral and clinical evaluation of two psychotropic agents: Doxepin-hydrochloride and perphenazine-amitriptyline hydrochloride. Psychosomatics 13: 125 (1972).

Nahunek, K.; Kamenicka, V.; Ceskova, E.; Rodova, A.; Svestka, J. and Misurek, J.: Clinical experience with doxepin. Activitas Nervosa Superior 16: 185 (1974).

Nixon, D.D.: Thrombocytopenia following doxepin treatment. Journal of the American Medical Association 220: 418 (1972).

Noguchi, Y.; Sakai, T.; Ishiko, J. and Sugimoto, S.: Acute toxicity of doxepin hydrochloride. Pharmacometrics (Tokyo) 6: 889-897 (1972a).

Noguchi, Y.; Sakai, T. and Arakawa, M.: Subacute toxicity of doxepin hydrochloride in rats. Pharmacometrics (Tokyo) 6: 899-928 (1972b).

Noguchi, Y.; Sakai, T. and Arakawa, M.: Chronic toxicity of doxepin hydrochloride in rats. Pharmacometrics (Tokyo) 6: 929-954 (1972c).

Norheim, G.: Determination of doxepin in autopsy material. Archiv fur Toxikologie 31: 7 (1973).

Nurowska, K. and Welbel, L.: Efficacy of dibenzepin, doxepin, and chlorimipramine in depression. Psychiatrie Polska 7: 69-74 (1973).

Oates, J.A.; Fann, W.E. and Cavanaugh, J.H.: Effect of doxepin on the norepinephrine pump. A preliminary report. Psychosomatics 10 (Section II): 12 (1969).

Oliver, J.S. and Watson, A.A.: Doxepin poisoning. Medicine, Science, and the Law 14: 280 (1974).

Otsuki, I.; Ishiko, J.; Sakai, M.; Shimahara, K. and Momiyama, T.: General pharmacological effects of doxepin hydrochloride: A psychotropic agent. Folia Pharmacologia Japonica 68: 762 (1972a).

Otsuki, I.; Ishiko, J. and Sakai, M.: Comparison of the pharmacologic activities of doxepin hydrochloride with those of its geometric isomers. Pharmacometrics (Tokyo) 6: 973-984 (1972b).

Owaki, Y.; Momiyama, H. and Onodera, N.: Effects of doxepin hydrochloride administered to pregnant rats upon the fetuses and their postnatal development. Pharmacometrics 5: 913 (1971).

Pebay-Peyroula, F.; Bismuth, C. and Autret, A.: Premier cas francais d'intoxication aigue par la doxepin. Journal European de Toxicologie 2: 77 (1969).

Pereira, C.J.L. and Lipke, C.P.R.: Preliminary results from an eight months trial of a single agent — doxepin/electro-

encephalographic study of 32 patients. Folha Medica (Brazil) 60: 51 (1970).

Pitts, N.E.: The clinical evaluation of doxepin — a new psychotherapeutic agent. Psychosomatics 10: 164 (1969).

Poeldinger, W.: Zur Methodik der Entwicklung und Prufung neuer Antidepressiva. Der Nervenarzt 37: 121 (1966a).

Poeldinger, W.: Vergleichende klinische Erfahrungen mit neuen trizyklischen Psychopharmaka. Therapeutische Umschau 23: 373 (1966b).

Poeldinger, W. and Peter, J.: Wirkungsspektren und Indikationen des Doxepins. Praxis 59: 1006 (1970).

Poeldinger, W., Angst, J., Cornu, F.; Dick, P. and Heimann, J.: Therapeutische Erfahrungen an funf Kliniken mit einen Dibenzoxepin — Derivat bei depressionen Zustandsbilden. Arzneimittel-Forschung 16: 650 (1966).

Popovic, M. et al.: Our experiences with doxepin in the treatment of depressive states. Anal. Zavoda Mentalno Zdravlje (Belgrade) 2: 25 (1970).

Prange, A.J.: The use of antidepressant drugs in the elderly patient; in Eisdorfer and Fann (Eds) Psychopharmacology and Aging, p.224 (Plenum, New York 1973).

Querol, M.: Double blind study with anti-depressants. Revista de Neuro-Psiquiatria 33: 251 (1970).

Radmayr, E.: Attempted suicide with doxepin. Osterreich Monatschafte fur azztliche Fortbildung und pharmazeutische Dokumentation 12: 155 (1971).

Radmayr, E.: Langzeittherapie mit Sinquan. Medizinische Welt 27: 446 (1976).

Rapado, A.: Double blind clinical trial of doxepin and placebo in a general medical clinic. Medicine et Hygiene 27: 1426 (1969).

Raskind, M.A.; Alvarez, C.; Pietrzyk, M.; Westerlund, K. and Herlin, S.: Helping the elderly psychiatric patient in crisis. Geriatrics 6: 51 (1976).

Renshaw, D.C.: Doxepin treatment of sexual dysfunctions associated with depression; in Mendels (Ed) Sinequan: A monograph of recent clinical studies, p.23 (Excerpta Medica, Amsterdam 1975).

Ribbentrop, A. and Schaumann, W.: Pharmakologische Untersuchungen mit Doxepin, einem Antidepressivum mit zentral anticholinerger und sedierender Wirkung. Arzneimittel-Forschung 15: 863 (1965).

Rickels, K.; Hutchison, J.C.; Weise, C.C.; Csanalosi, Irma; Chung, H.R. and Case, W.G.: Doxepin and amitriptyline-perphenazine in mixed anxious-depressed neurotic outpatients. A collaborative controlled study. Psychopharmacologia 23: 305 (1972).

Rickels, K.; Perloff, M.; Stepansky, W.; Dion, H.S.; Case, W.G. and Sapra, R.K.: Doxepin and diazepam in general practice and hospital clinic neurotic patients. A collaborative controlled study. Psychopharmacologia 15: 265 (1969).

Roth, J.A.: Inhibition of rabbit monoamine oxidase by doxepin and related drugs. Life Sciences 16: 1309 (1975).

Ruiz Taviel de Andrade, A.: Twenty-five cases of anxiety/depression treated with doxepin hydrochloride. Revista Medicina (Mex) 51: 164 (1971).

Saarnivaara, L. and Mattila, M.J.: Comparison of tricyclic antidepressants in rabbits: Antinociception and potentiation of the noradrenaline pressor responses. Psychopharmacologia 35: 221 (1974).

Sanger, M.D.: The treatment of anxiety and depression in the allergic patient. Annals of Allergy 27: 506 (1969a).

Sanger, M.D.: Depression and allergic dermatologic disease. Psychosomatics 10 (Section II): 25 (1969b).

Schaumann, Von, W. and Ribbentrop, A.: Interferenz der zentralen anticholinergen Wirkung bei der tierexperimentellen Prufung potentieller Antidepressiva. Arzneimittel Forschung 16: 646 (1966).

Schildkraut, J.J.: Neuropsychopharmacology and the Affective Disorders (Little Brown, Boston 1970).

Schreiber, F.K.: Doxepin in functional heart complaints and other organic diseases. Medizinische Klinik 65: 1920 (1970).

Seppala, T.; Linnoila, M.; Elonen, E.; Mattila, M.J. and Maki, M.: Effect of tricyclic antidepressants and alcohol on psychomotor skills related to driving. Clinical Pharmacology and Therapeutics 17: 515 (1975).

Silva, G.R. and Signes, G.E.: Evaluacion clinica de la doxepina en pacientes con reaccion depresiva (Experiencia doble-ciego). Revista Medica de Chile 100: 257 (1972).

Sim, M.; Bindman, E.; Conochie, B.C. and Sandilands, D.W.J.M.: The treatment of anxiety/depressive states. A comparative trial of doxepin (Sinequan) with chlordiazepoxide (Librium). Clinical Trials Journal 1: 22 (1971).

Simeon, J.; Spero, M. and Fink, M.: Clinical and EEG studies of doxepin. Psychosomatics 10 (Section II): 14 (1969).

Simeon, J.; Spero, M.; Nikolovksi, O.T. and Fink, M.: A comparison of doxepin and chlordiazepoxide in the therapy of anxiety. Current Therapeutic Research 12: 201 (1970).

Simpson, F.O.: Hypertensive disease; in Avery (Ed) Drug Treatment, p.500 (ADIS Press, Sydney; Publishing Sciences Group, Acton, Mass., Churchill Livingstone, Edinburgh 1976).

Smith, A.; Traganza, E. and Harrison, G.: Studies on the effectiveness of antidepressant drugs. Psychopharmacology, Special Issue; Psychopharmacology Research Branch, National Institute of Mental Health, Chevy Chase, March (1969).

Smith, J.A. and Renshaw, D.C.: Insomnia, a signal symptom. Presented at the 127th Annual Meeting of the American Psychiatric Association, Detroit, May (1974).

Smith, M.E.: A controlled comparative study of doxepin and chlordiazepoxide in psychoneurotic anxiety. Journal of Clinical Pharmacology 11: 152 (1971).

Solis, H.G.; Molina, G.B. and Pineyro, A.: Clinical evaluation of doxepin and amitriptyline in depressed patients. Current Therapeutic Research 12: 524 (1970).

Spaulding, P.E.: Pseudodementia in the nursing home. Scientific exhibit. Pfizer Laboratories (1976).

Spensley, J.: Doxepin: A useful adjunct in the treatment of heroin

addicts in a methadone programme. International Journal of The Addictions 11: 191 (1976).

Steen, S.N. and Thomas, J.S.: The effects of doxepin, separately and combined with meperidine, on the human respiratory centre. IRCS Medical Science 1: 3 (1973).

Sterlin, C.; Ban, T.A.; Lehmann, H.E. and Jarroid, L.: A comparative evaluation of doxepin and chlordiazepoxide in the treatment of psychoneurotic outpatients. Current Therapeutic Research 12: 195 (1970).

Sterlin, C.; Oliveros, R.; Ban, T.A. and Jarrold, L.: Doxepin in the treatment of psychoneurotic inpatients. Current Therapeutic Research 13: 580 (1971).

Sterlin, C.; Ban, T.A. and Jarrold, L.: The place of doxepin among the anxiolytic-sedative drugs. Current Therapeutic Research 14: 195 (1972a).

Sterlin, C.; Ban, T.A.; Lehmann, H.E. and Jarrold, L.: Doxepin in the treatment of hospitalised and ambulatory psychoneurotic patients. International Journal of Clinical Pharmacology 6: 256 (1972b).

Souza, A.D.: Double blind study of doxepin in anxiety. A Folha Medica 62: 105 (1971).

Tadokoro, S.: Behavioral-pharmacological studies on doxepin, a tricyclic psychotropic agent. 1. Changes of conditioned behavior after a single dose of doxepin. Folia Pharmacologica Japonica 68: 536 (1972a).

Tadokoro, S.: Behavioral-pharmacological studies on doxepin, a tricyclic psychotropic agent. 2. Changes of conditioned behavior after repeated doses of doxepin. Folia Pharmacologica Japonica 68: 548 (1972b).

Tehrani, J.B.; Rossi, G.V. and Goldstein, F.J.: Doxepin and imipramine: Effect on catecholamine inhibition of ganglionic transmission. Life Sciences 17: 257 (1975).

Toru, M.; Takamizawa, M.; Kariya, T.; Kobayashi, K. and Takahashi, R.: A double-blind sequential comparison of doxepin with amitriptyline in depressed patients. Psychosomatics 13: 241 (1972).

Traitz, J.J.; Blaine, G. and Georgia, E.H.: Evaluation of gastrointestinal symptomatology in psychoneurotically depressed outpatients. Presented at the Southern Medical Association, 79th Annual Meeting, New Orleans (November 1976).

Trappe, B.: Doxepin and amitriptyline-chlordiazepoxide combination in neurotic states. A comparative double-blind trial. Current Medical Research and Opinion 2 (Suppl): 71 (1975).

Tuomisto, J.: A new modification for studying 5-HT uptake by blood platelets: A re-evaluation of tricyclic antidepressants as uptake inhibitors. Journal of Pharmacy and Pharmacology 26: 92 (1974).

Van Praag, H.M.: Screening and evaluation of antidepressives. Geneesk Gids 2: 51 (1969).

Van Riezen, H. and Delver, A.: The effect of a number of drugs with different pharmacological properties upon reserpine-induced hypothermia in mice. Arzneimittel-Forschung 21: 1562 (1971).

Vitorovic, M. and Zvan, V.: Our first experience with the new antidepressive medicament doxepin (Sinequan-Pfizer). Medical Journal of Slovenia (Yugoslavia) 39: 129 (1970).

Vohra, J.; Burrows, G.; Hunt, D. and Sloman, G.: The effect of toxic and therapeutic doses of tricyclic antidepressant drugs on intracardiac conduction. European Journal of Cardiology 3: 219 (1975b).

Vohra, J.; Burrows, G.D. and Sloman, G.: Assessment of cardiovascular side-effects of therapeutic doses of tricyclic antidepressant drugs. Australia and New Zealand Journal of Medicine 5: 7 (1975a).

Vohra, J.; Hunt, D.; Burrows, G.D. and Sloman, G.: Intracardiac conduction defects following overdose of tricyclic antidepressant drugs. European Journal of Cardiology 2/4: 453 (1975c).

Wiener, K.: Ergebnisse einer klinischen Pruefung von Doxepin bei Asthma bronchiale. Medizinische Welt 22: 1343 (1971).

Williams, J.O.: Respiratory depression in tricyclic overdosage. British Medical Journal 1: 631 (1972).

Wohlfarth-Ribbentrop, A. and Schaumann, W.: Tierexperimentelle Vergleich der tranquili siereiden Wirkung von Doxepin mit bekamten Psychopharmaka. Arzneimittel-Forschung 19: 2012 (1969).

Woody, G.E.; O'Brien, C.P. and Rickels, K.: Depression and anxiety in heroin addicts: A placebo-controlled study of doxepin in combination with methadone. American Journal of Psychiatry 132: 447 (1975).

Zielinski, M.; Janiec, W. and Herman, Z.S.: Central action of (1-(3-dimethyl-aminopropylidene)-6,11-dihydrodibenzo [b,e]oxepine hydrochloride (Doxepin). Polish Journal of Pharmacology and Pharmacy 25: 17 (1973).

Author's address: *R.M. Pinder, R.N. Brogden, T.M. Speight and G.S. Avery*, Australasian Drug Information Services, P.O. Box 34-030, Birkenhead, *Auckland 10* (New Zealand).